Trans-1,3-dithiane-1,3-dioxide, a chiral carbonyl anion equivalent

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TRANS-1,3-DITHIANE-1,3-DIOXIDE,

A CHIRAL CARBONYL ANION EQUIVALENT.

Submitted by

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Of the University of Bath

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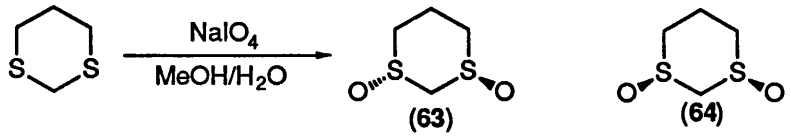
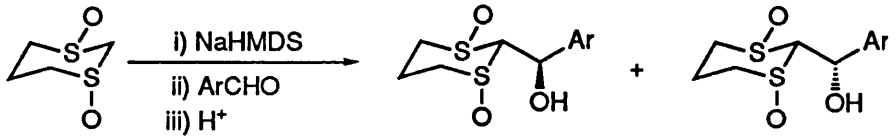
ABSTRACT.

An investigation of *trans*-1,3-dithiane dioxide, (**63**) as a chiral carbonyl anion equivalent is described. Stereoselective oxidation (70-80% d.e.) of 1,3-dithiane with sodium periodate is a convenient synthesis of the thermodynamically more stable *trans* dioxide (**63**), in racemic form.



(63) (64)

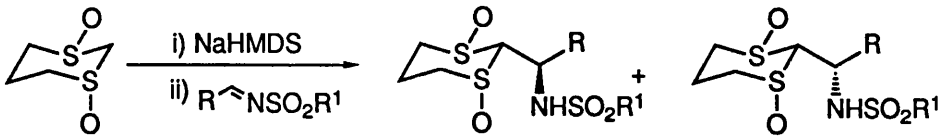
Anions of (**63**) can be generated with ^{n}butyllithium or HMDS bases and subsequent addition to aldehydes gives diastereomeric mixtures of adducts. The diastereoselectivity of these reactions is dependent upon three main factors; the reaction temperature, the metal counter-ion and the aldehyde used. Excellent diastereoselectivities (typically 95:5 **a:b**) can be obtained under equilibrating conditions at 0 °C with Na-(**63**) and a range of aromatic aldehydes.



(63) (a) (b)

Aliphatic aldehydes give variable selectivities (0-70% d.e.) under these conditions. Under kinetic control at -78 °C selectivities are poor (0-50% d.e.) in most cases. An exception is the addition of Zn-(**63**) to benzaldehyde which gave the adducts with a 86% d.e. in favour of isomer (**b**). The reason for the high selectivity in reactions of Na-(**63**) and aromatic aldehydes is not clear. Crown ether experiments indicate that a Na chelate is not involved and reactions with a variety of 2,6-disubstituted aromatic aldehydes also suggest that an *ortho* hydrogen on the aromatic ring is important.

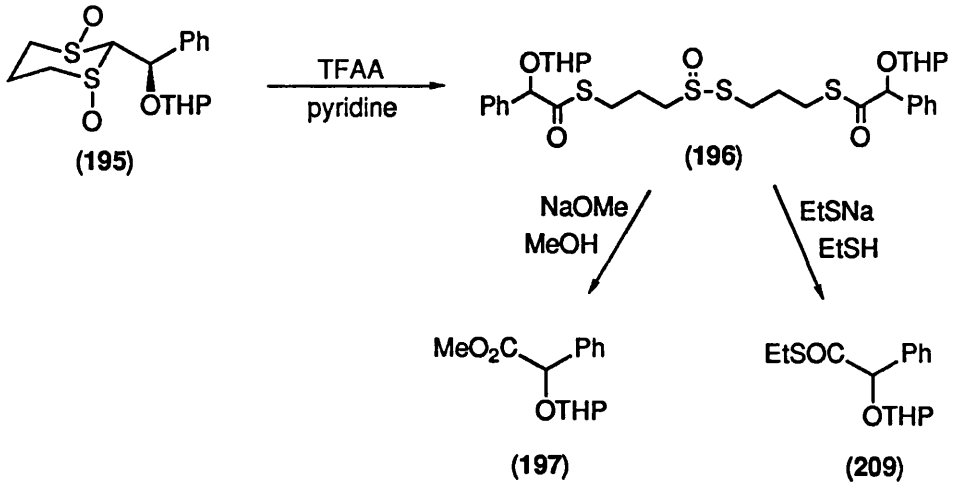
The addition of anions of (**63**) to non-enolizable imines was also investigated. *N*-Sulphonyl imines give moderate yields of adducts with variable selectivities (6-70% d.e.).



(63)

The reactions appear to be under kinetic control and equilibration of the adducts does not occur at temperatures up to 20 °C.

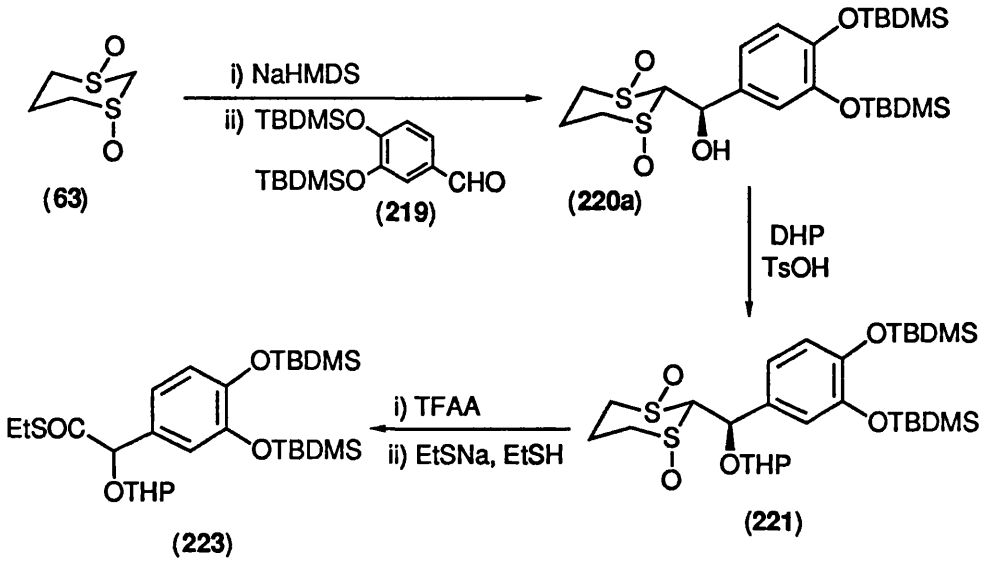
Hydrolysis of the dithiane dioxide moiety was achieved by Pummerer reaction of the THP protected benzaldehyde adduct (**195**) with TFAA.



(195) (196) (197) (209)

The product (**196**), formed by dimerization of an intermediate sulphenic acid, can be converted into the methyl ester (**197**) or the thiolester (**209**) by treatment with sodium methoxide or sodium ethanethiolate respectively. In the optically active series some racemization occurs during the hydrolysis sequence to the methyl ester (RR)-(RS)_(**197**), which was produced in 80% e.e. No racemization occurs in the preparation of the thiolester (**209**). After deprotection of the alcohol chiral shift NMR analysis indicated an optical purity of >95% e.e.

The application of this methodology towards the asymmetric synthesis of 3,4-dihydroxymandelic acid is described.



In the racemic series the adduct (**220a**) can be produced selectively (92% d.e.) by addition of Na-(**63**) to the aldehyde (**219**). Protection of the alcohol and hydrolysis gives (**223**), a derivative of the target compound.

CONTENTS

Abbreviations.

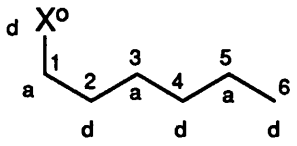
Ac	Acetyl.
d.e.	Diastereomeric excess.
DET	Diethyltartrate.
DHP	Dihydropyran.
DIBAL	Diisobutylaluminiumhydride.
DME	Dimethoxyethane.
DMF	Dimethylformamide.
DMSO	Dimethylsulphoxide.
e.e.	Enantiomeric excess.
HMDS	Hexamethyldisilazide.
HPLC	High Pressure Liquid Chromatography.
LDA	Lithium diisopropylamide.
MCPBA	*Meta*-Chloroperbenzoic acid.
NMR	Nuclear magnetic resonance.
OXONE	Potassium peroxymonosulphate.
py	Pyridine.
SES	(β-(trimethylsilyl)ethyl)sulphonyl.
TBDMS	*tert*-Butyldimethylsilyl.
TFAA	Trifluoroacetic anhydride.
TFAE	Trifluoroanthrylethanol.
THF	Tetrahydrofuran.
THP	Tetrahydropyran.
tlc	Thin layer chromatography.
TMP	Tetramethylpiperidide.
TMS	Trimethylsilyl.
Ts	*p*-Toluenesulphonyl

The sulphoxide bond is shown as S-O with the S^+ and O^- charges omitted, except for cases when the charged atoms are specifically involved in a mechanism.

CHAPTER 1. CARBONYL ANION EQUIVALENTS.

1.1 Introduction.

The reactions most frequently used in organic synthesis are polar in nature, i.e. nucleophilic, or donor, and electrophilic, or acceptor, sites are used to make or break bonds. The heteroatoms, usually oxygen or nitrogen, contained in a molecule determine the reactivity of the carbon skeleton. These heteroatoms impose an alternating acceptor and donor reactivity pattern, i.e. acceptor properties at carbons $C^{1.3.5...}$, and donor properties at carbons $C^{2.4.6...}$, the heteroatom X^o itself is a donor centre.

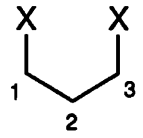


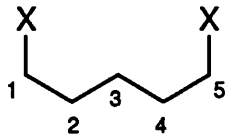
a; acceptor
d; donor

X; O,N

Figure 1

As a consequence, and synthetic limitation, the combination of components with this reactivity leads only to 1,3-, 1,5-,...1,(2n+1)-disubstituted products. (i.e. Odd numbers of carbon atoms between functional groups.)

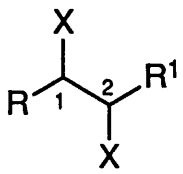


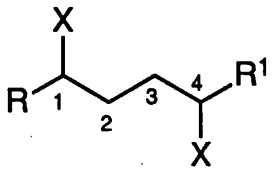


X; O,N

Figure 2

This "normal reactivity" does not enable constrution of 1,2n-disubstituted products. (i.e. Even numbers of carbon atoms between functional groups.)





X; O,N

Figure 3

Synthesis of these types of compound require a reagent in which the acceptor or donor centres are reversed as compared to the "normal reactivity", i.e. "reactivity umpolung".[1]

As the premier functionality in organic synthesis, the carbonyl group is intimately involved in many carbon-carbon bond forming reactions. The electronegativity of oxygen polarises the carbon-oxygen bond, making the carbon atom an acceptor, and the oxygen a donor, i.e. the "normal reactivity" as described above. This reactivity is such that the carbonyl provides acyl cation (1) and enolate anion (2) equivalents.

(1) **(2)** **(3)** **(4)**

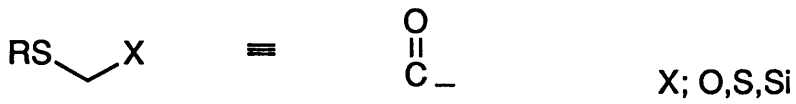
Figure 4

Reversal of this natural polarity of the carbonyl group leads to the umpoled equivalents, acyl anions (3) and enolate cations (4).

In the literature there are many examples of umpoled carbonyl reagents and the area has been the subject of several review articles[2]. In the following sections some of the basic classes of acyl, formyl and hydroxy carbonyl equivalents are described. Examples, where control of chirality is achieved are discused in more detail.

1.2 Acyl and Formyl Anion Equivalents.

In 1965 Corey and Seebach suggested that certain sulphur stabilised anions could be suitable for use as masked nucleophilic acylating reagents[3]. Many such reagents have now been successfully used to this end. These reagents have usually been of the type (**5**), figure 5, with a second heteroatom attached to the nucleophilic carbon.



(5)

Figure 5

Heteroatoms that have been used include oxygen[4], sulphur[5], selenium[6], silicon[7] and nitrogen[8]. The most commonly encountered reagent of this type is 1,3-dithiane, (**6**). Lithiated 1,3-dithiane, easily prepared by treatment with butyllithium, has been reacted with a variety of electrophiles including alkyl halides, alkyl *p*-toluene sulphonates, allyl halides, carbonyl compounds and α,β-unsaturated carbonyl compounds, with both 1,2 and 1,4 addition products obtainable, depending on conditions used. Hydrolysis of the dithioacetal then affords the carbonyl compounds, (**8**).

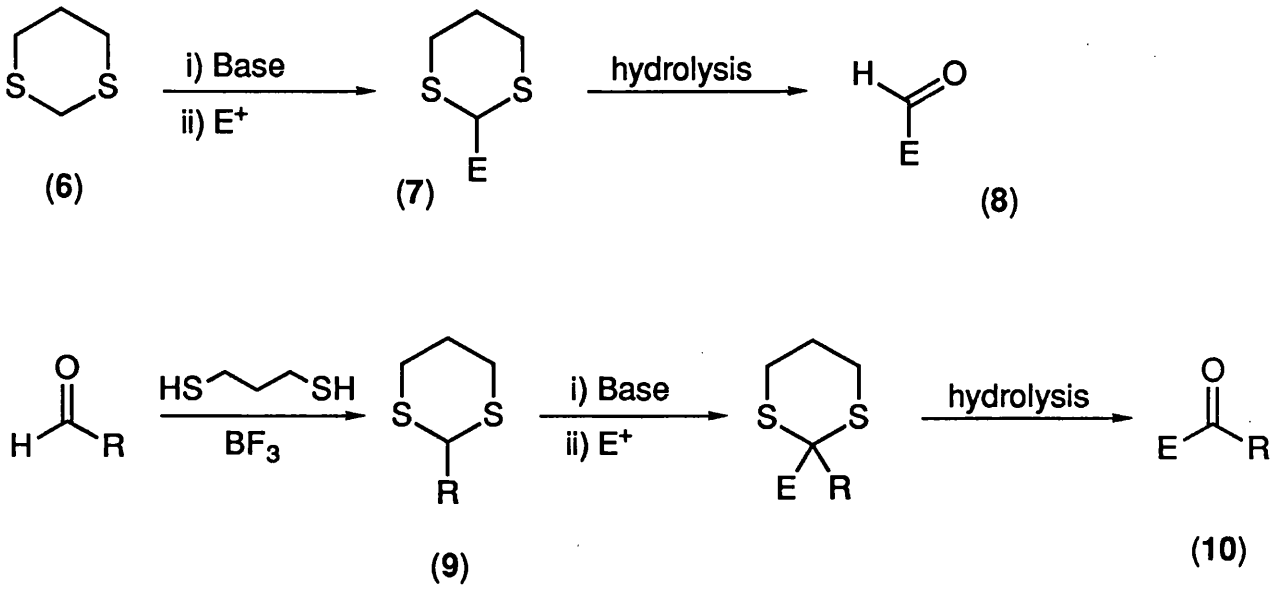


Figure 6

In this example 1,3-dithiane is acting as a formyl anion equivalent (O=C⁻H). 1,3-Dithianes can also be used as acyl anion equivalents, (O=C⁻Me). 2-Substituted 1,3-dithianes (**9**), can be reacted in the same manner to give ketone compounds, (**10**). 2-Substituted dithianes can be prepared by condensation of 1,3-propanedithiol with an aldehyde, or by alkylation of 1,3-dithiane. Most of the reagents in this class have been used as acyl (R = alkyl or aryl), figure 7, and formyl (R = H), anion equivalents.

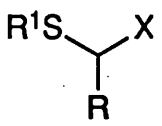
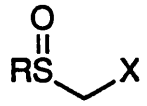


Figure 7

Another class of carbonyl anion equivalents are those stabilised by a sulphoxide (**11**).



(11)

Figure 8

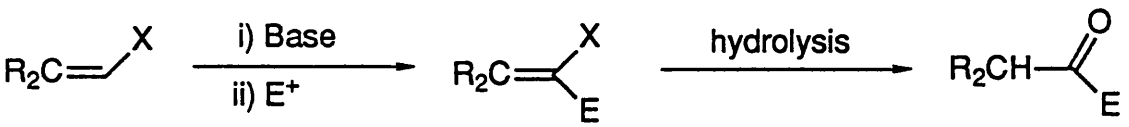
Due to the chiral nature of the sulphoxide, these can give rise to diastereomeric products and the possibility of chiral induction. These compounds will be discused under chiral carbonyl anion equivalents.

A third class of reagents are the vinyl compounds, (12).

(12)

Figure 9

The vinyl anion, of vinyl ethers[9], vinyl sulphoxides[10] and vinyl selenides[11], can be prepared by treatment with base. Addition of an electrophile and subsequent hydrolysis gives ketone products, (14).



(12) (13) (14)

Figure 10

1.3 Hydroxy Carbonyl Anion Equivalents.

There are three classical examples of hydroxy carbonyl equivalents that should be mentioned. The cyanide ion has been employed for decades in the conversion of halides to nitriles, and thence to carboxylic acids upon hydrolysis [12].

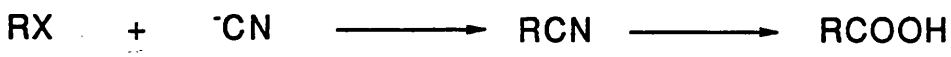


Figure 11

Trihalomethanes also represent $^{-}$COOH synthons. For example benzaldehyde and chloroform react in the presence of sodium ethoxide to give the α-hydroxy acid derivative[13], figure 12.

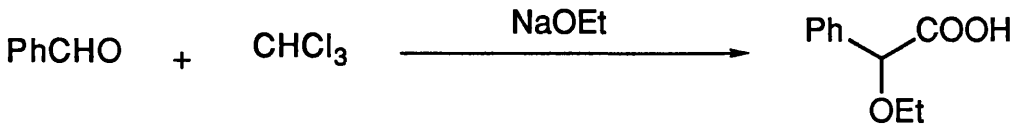


Figure 12

A third established method of umpoled carbonyl reactivity is the use of acetylene anions. Reaction with an aldehyde followed by oxidative cleavage also gives rise to α-hydroxy acids[14].

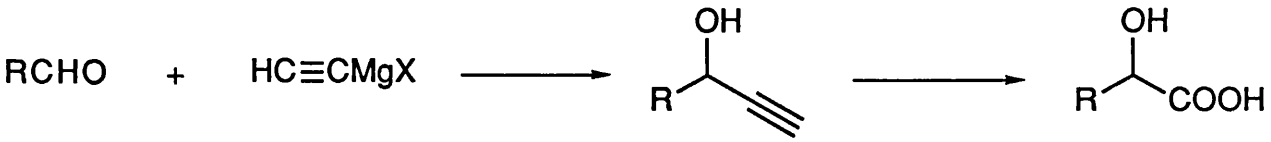


Figure 13

The many, more recent examples of hydroxy carbonyl anion equivalents[15], include the use of 2-trialkylsilyl substituted-1,3-dithianes, (**15**). Upon deprotonation, with butyllithium, and reaction with aldehydes or ketones, they give ketene thioacetals (**16**) which can be hydrolysed to carboxylic acids[16] (**17**), or α-halo esters[17] (**18**).

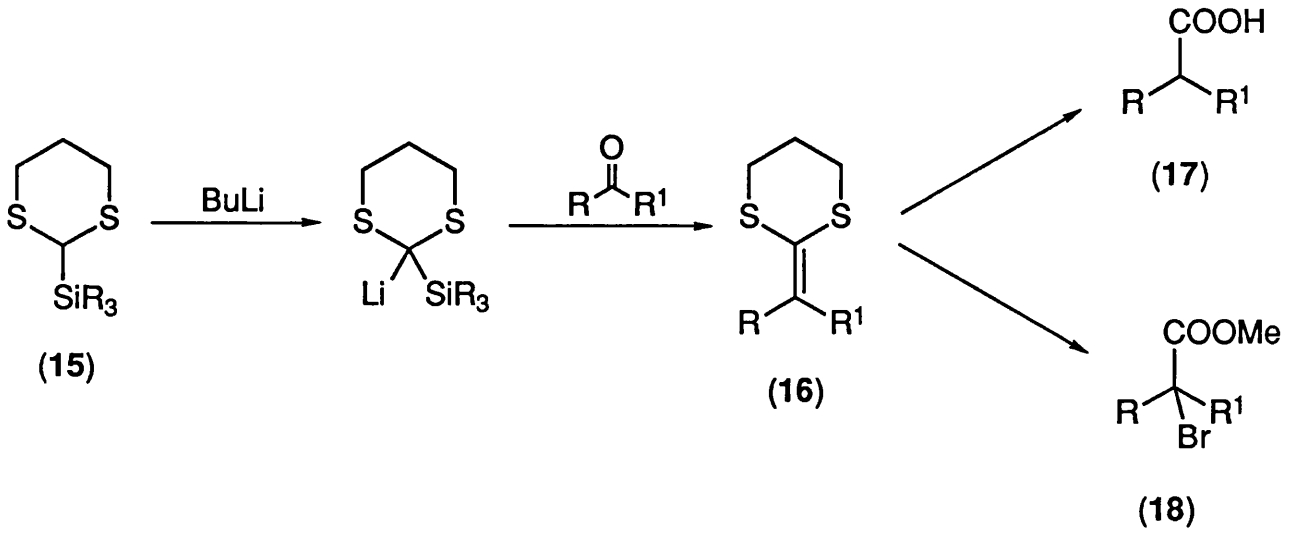


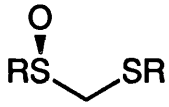
Figure 14

Sulphoxide stabilised carbanions have been used as hydroxy carbonyl synthons, examples where chiral induction is achieved will be discussed in the following section.

1.4 Chiral Carbonyl Anion Equivalents.

1.4.1 Sulphoxide Stabilised anions.

Several chiral carbonyl anion equivalents utilize the sulphoxide functionality to achieve asymmetric induction. Most of these reagents are of the type (**19**).

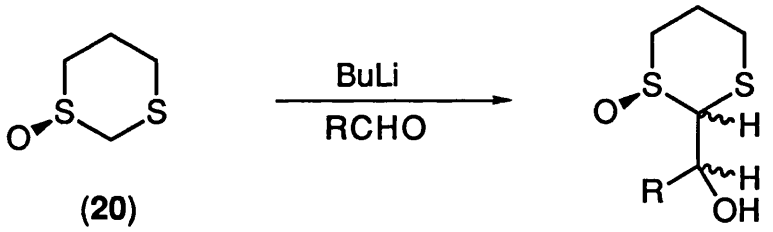


(19)

Figure 15

In the early 1970's methyl methylthiomethyl sulphoxide[18] (R=Me) and ethyl ethylthiomethyl sulphoxide[19] (R=Et) were used as acyl anion equivalents. However, no study was made of the possibility of chiral induction with these reagents.

The reactions of 1,3-dithiane-1-oxide (**20**), were first investigated by Helquist[20] in 1968, again no attempt at achieving chiral induction was made. Carey carried out a more thorough investigation of this reagent[21].



(20) **(21)**

Figure 16

Complex mixtures of diastereomers (**21**) were formed in reactions with aldehydes, with little selectivity. More recently, Fang[22] has reported the reactions of 2-propenyl-1,3-dithiane-1-oxide, (**22**). The allyl lithium (**23**) was generated with LDA, and reacted with a variety of aliphatic and aromatic aldehydes. Reactions were highly α-regioselective. The stereochemistry at the 2-position of the dithiane was exclusively *syn*. Selectivity at the alcohol chiral centre,

however was modest, with diastereomers (24) produced with ratios of between approximately 1:1 to 2:1.

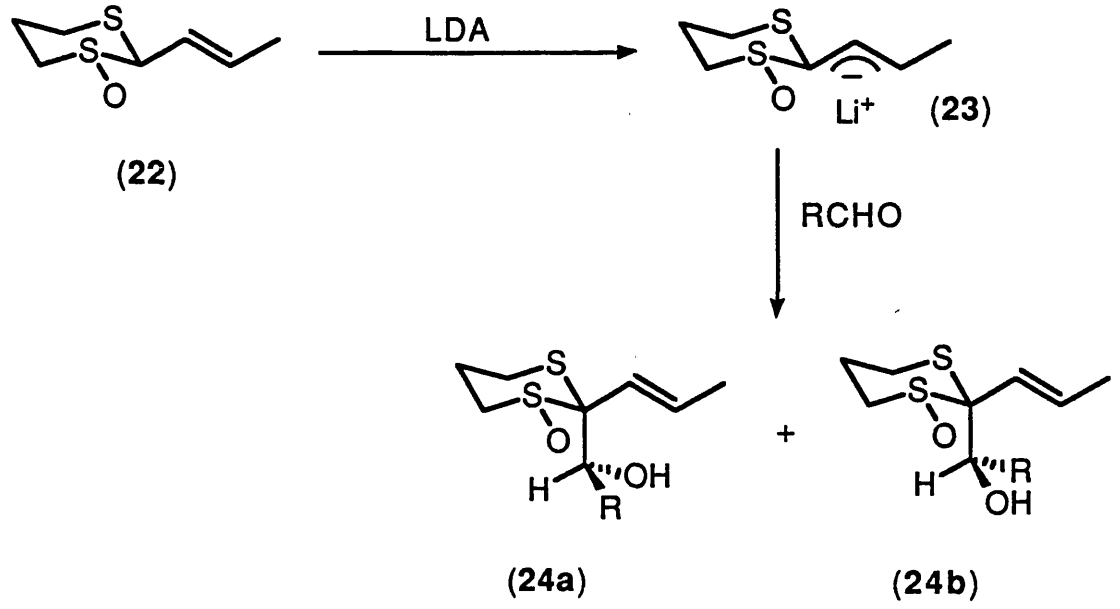


Figure 17

p-Tolyl *p*-tolylthiomethyl sulphoxide, (25) has been used as a chiral formyl anion equivalent by Scolastico *et al.*[23].

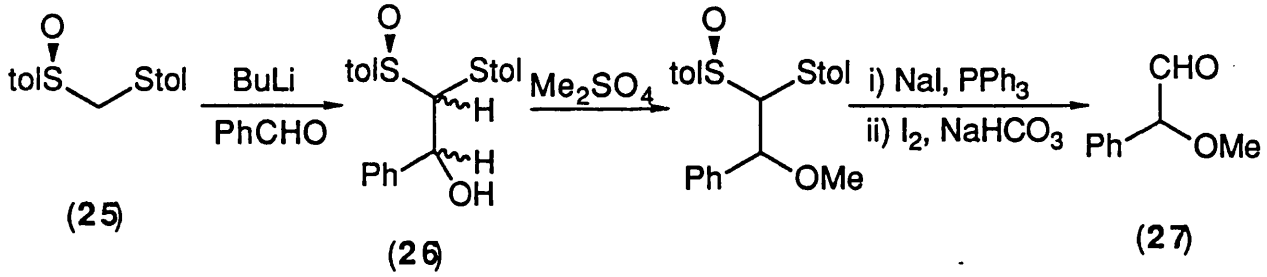


Figure 18

In the reaction with benzaldehyde, a mixture of three of the four possible diastereomers (26) were formed. These were not separated. Protection of the alcohol and hydrolysis led to the optically active α-hydroxy aldehyde derivative (27), with 70% enantiomeric excess.

1,4-Additions were also achieved with this reagent[24].

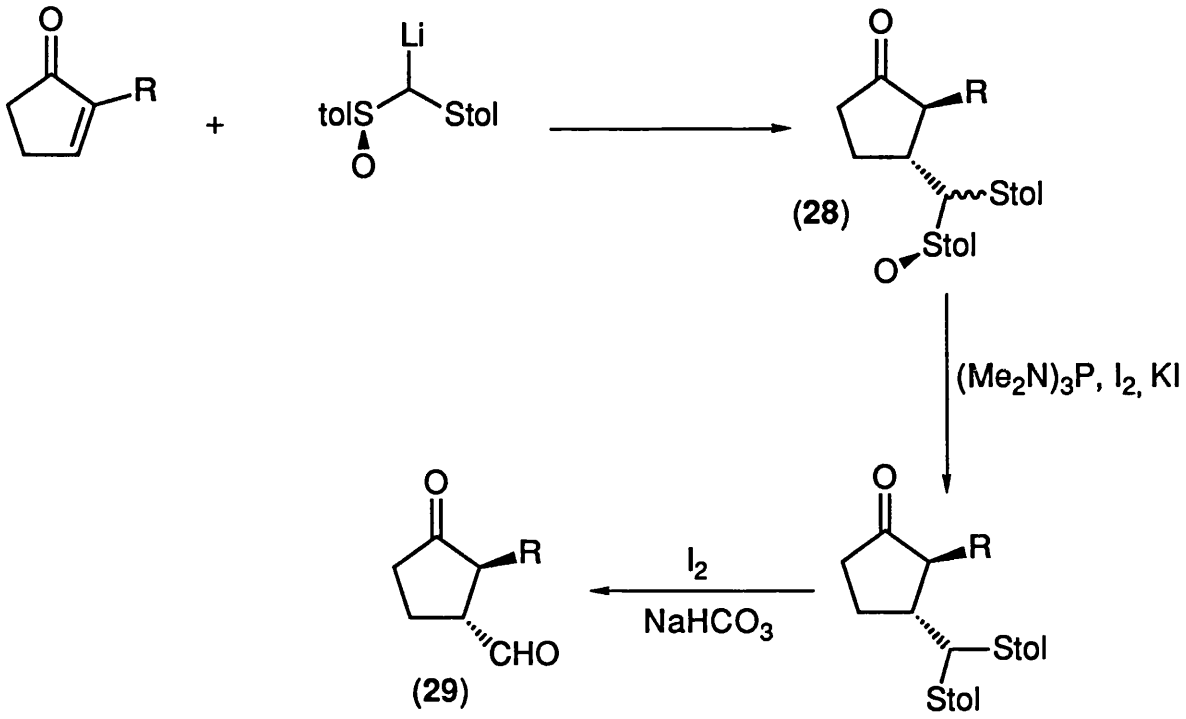
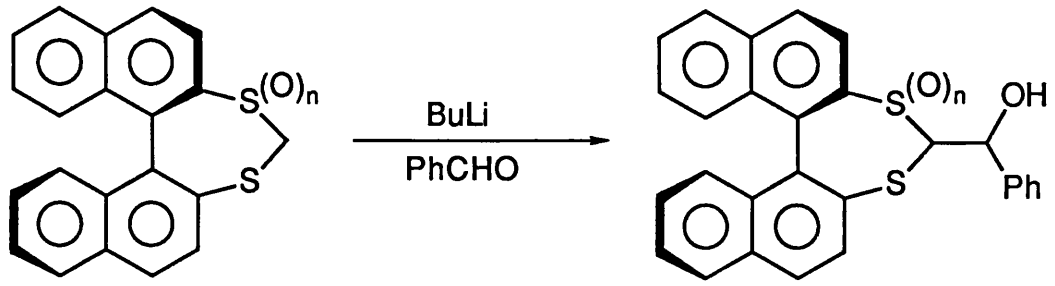


Figure 19

Four of the eight possible diastereomers were produced. The major diastereomeric pair (**28**), (92:8), could be separated. Reduction of the sulphoxide and dithioacetal hydrolysis gave (**29**) optically pure.

The chiral binaphthyl compounds (**30**) have been examined by DeLucchi and co-workers[25].



(30a) n=0
(30b) n=1

(31a) n=0
(31b) n=1

Figure 20

The C_2 symmetric dithioacetal (**30a**) reacted with butyllithium and benzaldehyde to give a 3:1 mixture of diastereomers. The monoxide (**30b**) gave just one of the four possible products. Hydrolysis of the adducts and reactions with other aldehydes have not been reported.

1-Chlorobutyl-*p*-tolylsulphoxide (**32**), has been used as a chiral carbonyl anion equivalent[26].

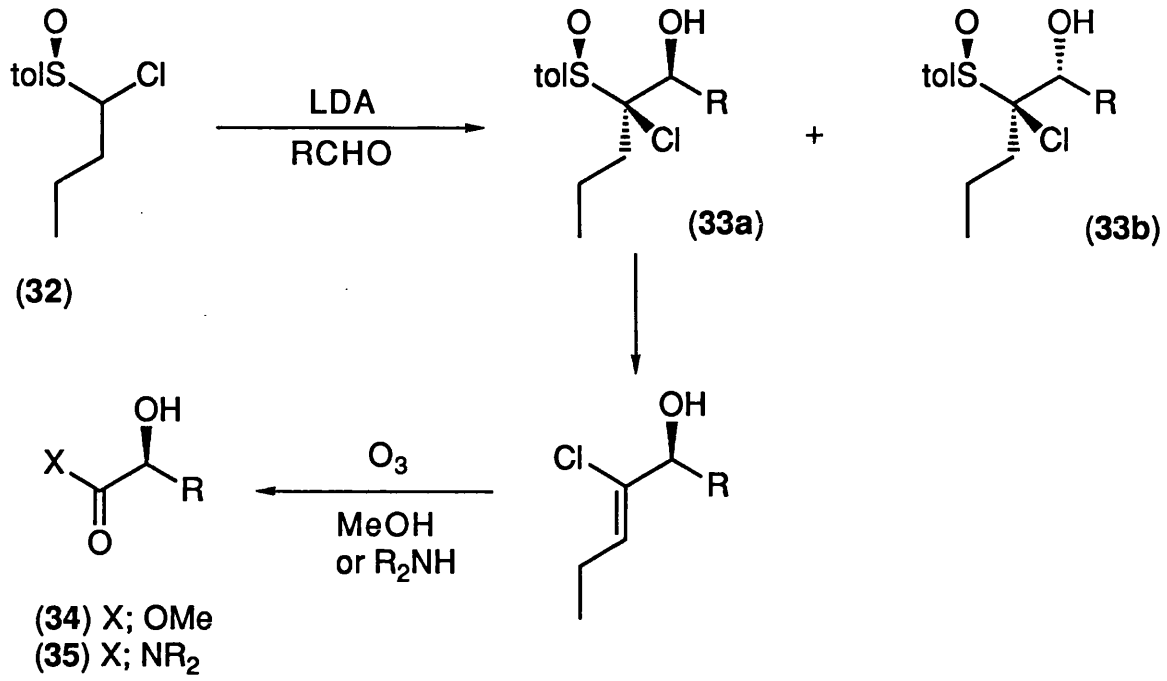


Figure 21

Poor selectivity was observed on reaction with aldehydes, approximately 1:1 ratios of diastereomers (**33**), were obtained. The diastereomers could be separated and sulphoxide elimination followed by ozonolysis gave the esters (**34**), or amides (**35**), with high optical purity.

Methyl *p*-tolylsulphoxide (**36**) has been employed in the asymmetric synthesis of α-hydroxy aldehyde derivatives by the methodology of Resnati[27].

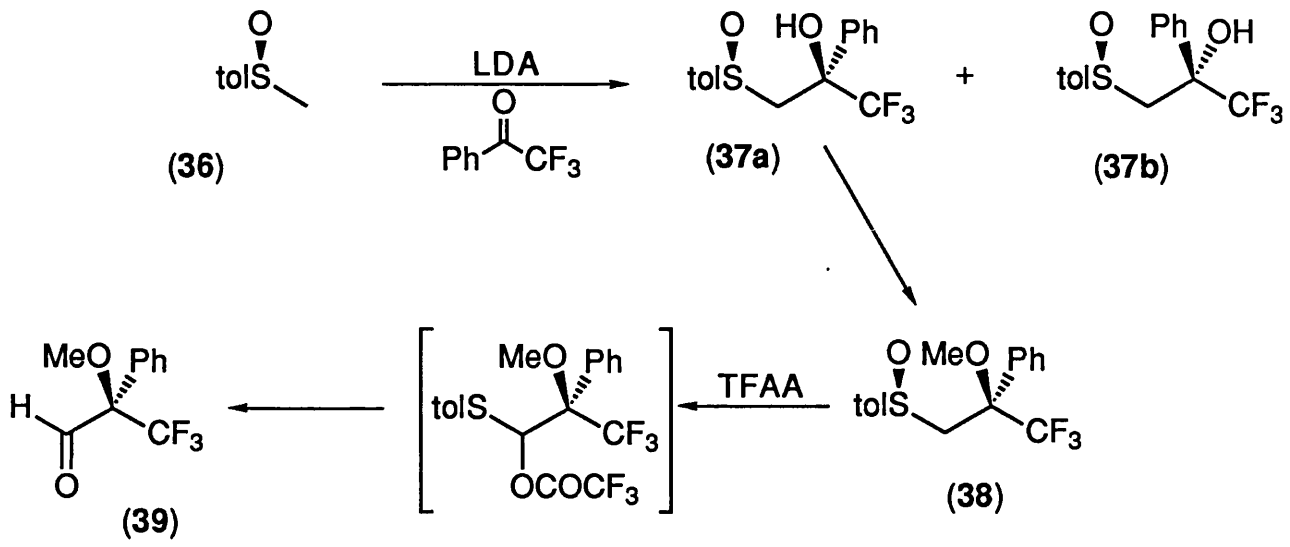


Figure 22

The LDA derived anion of (**36**) was reacted with trifluoroacetophenone to give a 3:1 ratio of separable diastereomers. The nucleophilic carbon atom of (**36**) is only at the alcohol oxidation level. However, after formation of the methyl ether (**38**), a Pummerer reaction with trifluoroacetic anhydride was used to transfer oxidation from the sulphoxide to this carbon atom to give the aldehyde (**39**).

Solladie has investigated the selectivity in the reactions of the β-disulphoxide, (S,S)-bis-*p*-tolylsulphinyl methane (**40**) with aldehydes[28].

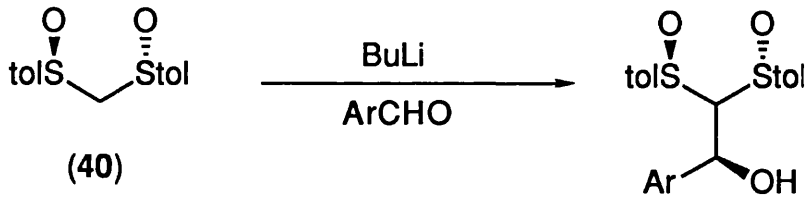


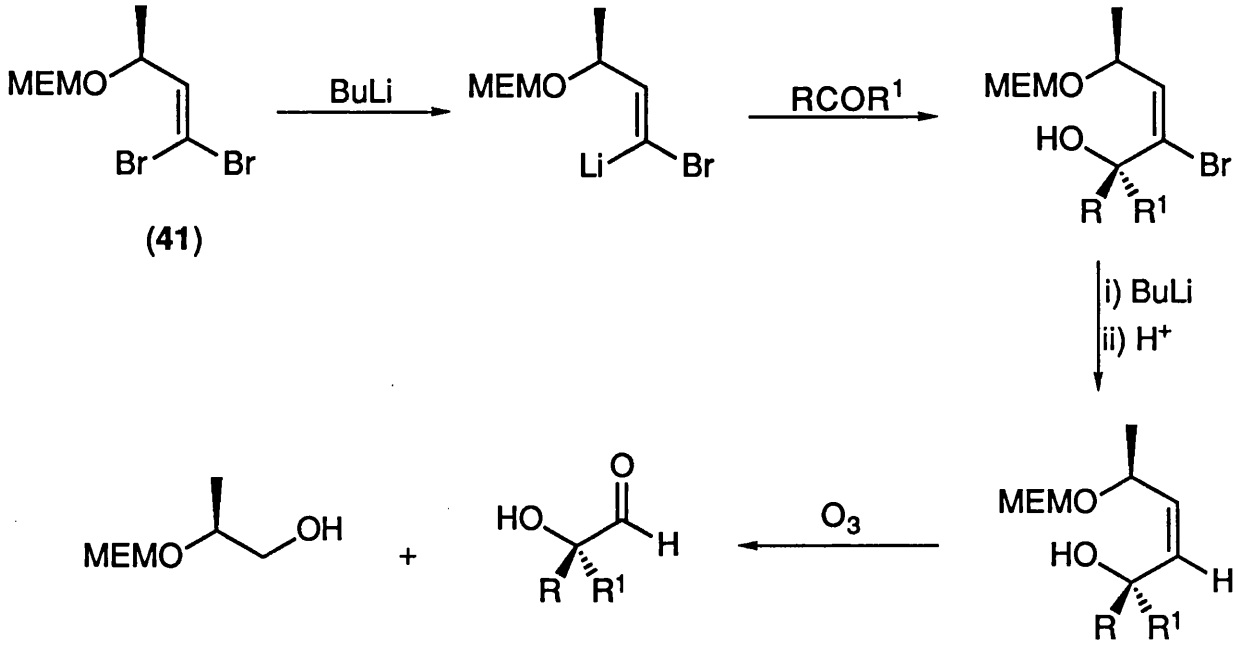
Figure 23

Good selectivities, (70-80% d.e.) were obtained with a variety of aromatic aldehydes. The presence of an electron donating group on the aromatic ring decreased the chemical yield, while two electron donating groups inhibited the reaction altogether. Aliphatic aldehydes gave poor selectivities (10-20% d.e.). No hydrolysis of this auxiliary has been reported.

1.4.2 Vinyl Chiral Carbonyl Anion Equivalents.

The vinyl dibromide reagent (**41**), derived from lactic acid, has been used as a chiral umpoled carbonyl equivalent[29].

Addition to prochiral carbonyl compounds gives good diastereoselectivities, (82-94% d.e.) with both aromatic aldehydes and ketones, and aliphatic aldehydes. Debromination and oxidative cleavage gave the α-hydroxy carbonyl compounds (**42**).

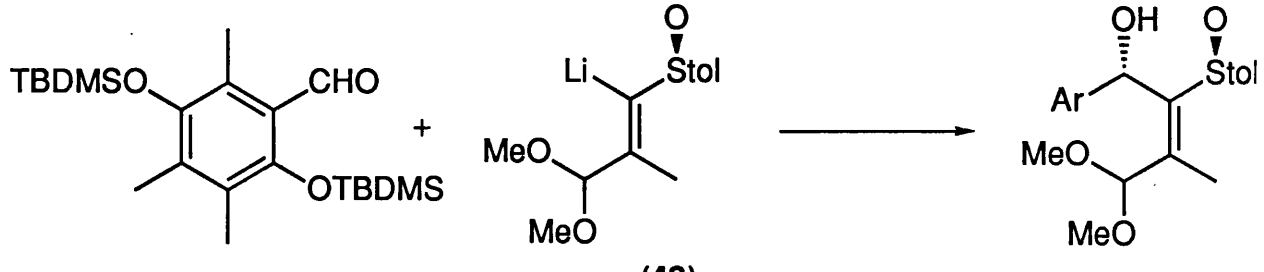


(**41**)

(**42**)

Figure 24

Vinyl sulphoxides have shown selectivity in reactions with aldehydes. A single isomer was obtained in the reaction of the lithiated vinyl sulphoxide (**43**) with an aromatic aldehyde[30].

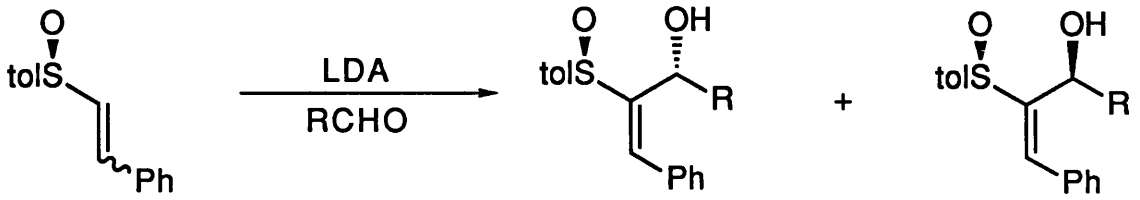


(**43**)

Figure 25

However, the vinyl sulphoxide functionality was not transformed into a carbonyl group.

Jenkins *et al.* have investigated the reactions of vinyl sulphoxide (**44**) with aliphatic aldehydes[31].



(44)

Figure 26

Selectivities ranged from 10-70% d.e., with larger R groups confering greater selectivity. No hydrolysis was reported.

1.4.3 Asymmetric Hydrocyanation.

There have been many reported attempts to realize asymmetric induction in the addition of HCN to carbonyl groups.

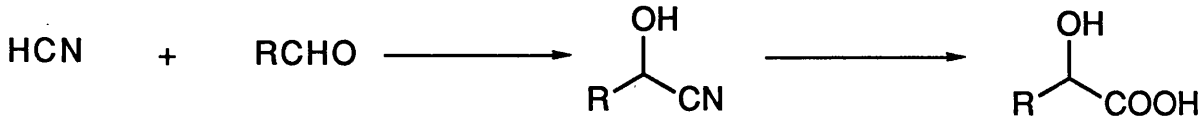
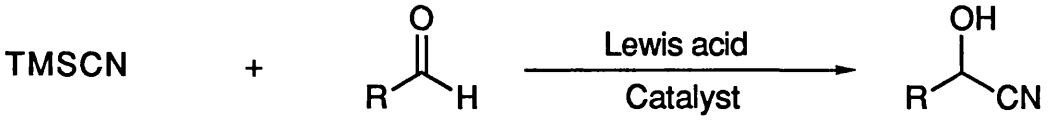


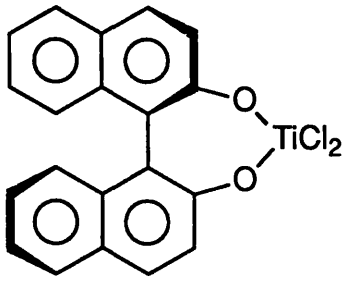
Figure 27

Reported methodologies include the use of alkaloids[32], poly(L-iminoisobutylethylene)[33] and cyclodextrin[34] as chiral catalysts, although the enantioselectivities obtained were low. The flavoprotein, D-oxynitrilase successfully catalysed the synthesis of a range of hydroxynitriles in good to excellent enantiomeric excess[35].

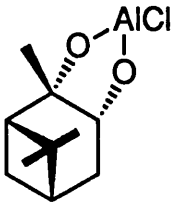
Chiral Lewis acids have also been used. Reetz has reported the use of the titanium (**45**), aluminium (**46**), and boron (**47**), species in the addition of TMSCN to aldehydes[36].

The most successful of these was the aluminium Lewis acid (**46**), which gave the cyanohydrin product of isobutyraldehyde with 82% e.e.

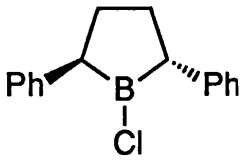




(**45**)



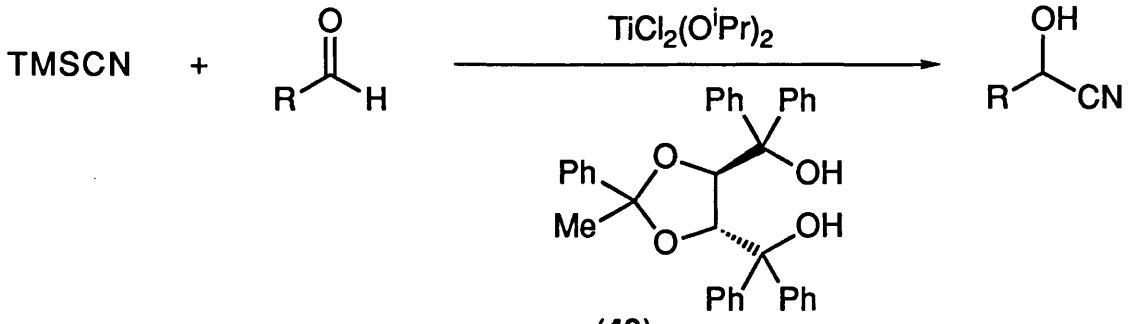
(**46**)



(**47**)

Figure 28

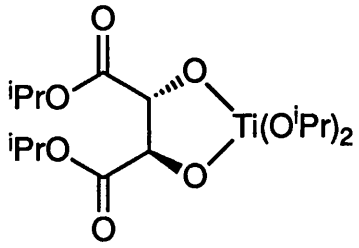
A chiral titanium (IV) complex, prepared *in situ* from a chiral diol (**48**) and dichlorodiisopropoxytitanium (IV), was employed by Narasaka *et al.*[37]. Hydrocyanation products were formed with 68-96% e.e.



(**48**)

Figure 29

A similar titanium Lewis acid (**49**) has been incorporated into to this reaction with aromatic aldehydes[38].



(49)

Figure 30

Optical purities of 60-91% e.e. were obtained.

Inoue and co-workers[39] have used a cyclic dipeptide (**50**) to catalyse the hydrocyanation reaction.

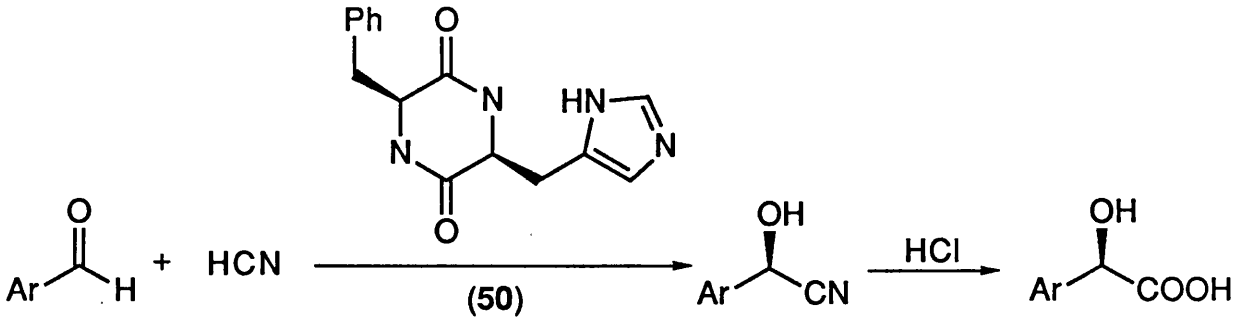


Figure 31

Moderate selectivities were obtained with aliphatic aldehydes, (18-71% e.e.). Aromatic aldehydes, except those with strong electron withdrawing groups, produced cyanohydrins with high optical purity (78-97% ee). Hydrochloric acid hydrolysis afforded the α-hydroxy acids, with no detectable racemization.

1.4.4 Asymmetric Direct Nucleophilic Acylation.

Direct nucleophilic acylation has been achieved by Enders and co-workers[40].

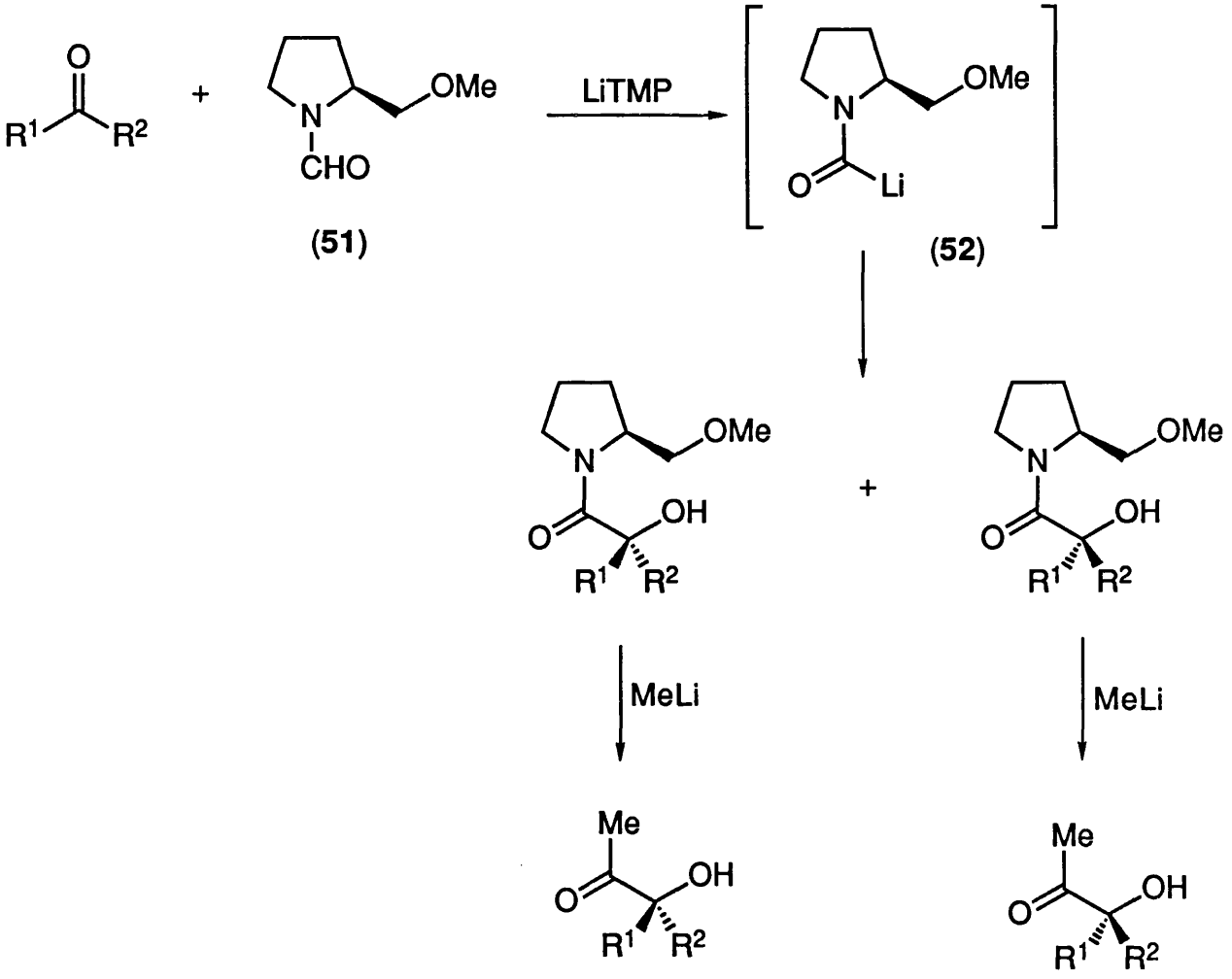


Figure 32

The highly reactive acyl anion (**52**), generated by treatment of (**51**) with lithium tetramethylpiperidide, was reacted with ketones. Selectivity in the addition was poor (5-20% d.e.). However, the diastereomeric adducts could be separated and treated with methyllithium to give the optically pure α-hydroxy ketones.

1.4.5 Additions To Acylated Chiral Carbonyl Equivalents.

The addition of chiral carbonyl anion equivalents to prochiral electrophiles often leads to mixtures of products with poor control of selectivity. To overcome this problem an alternative strategy has become widely adopted, figure 33.

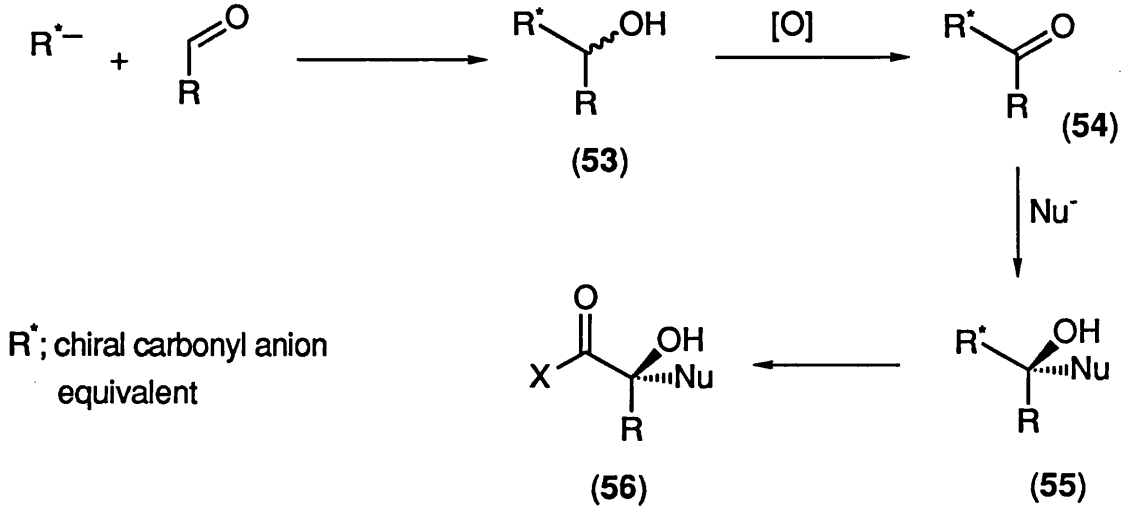


Figure 33

The chiral group R*, has been used to control the nucleophilic addition to carbonyl compounds (**54**), produced by oxidation of the diastereomeric mixture of adducts, (**53**). This procedure has led to the synthesis of α-hydroxy carbonyl compounds (**56**), with control of the configuration at the new stereocentre, despite lack of control in the initial anion addition to the aldehyde.

Eliel first introduced this approach in the asymmetric synthesis of α-hydroxy aldehydes using 1,3-oxathianes as chiral auxiliaries[41].The pulegone derived oxathiane (**57**), was found to be the most effective system[42], figure 34.

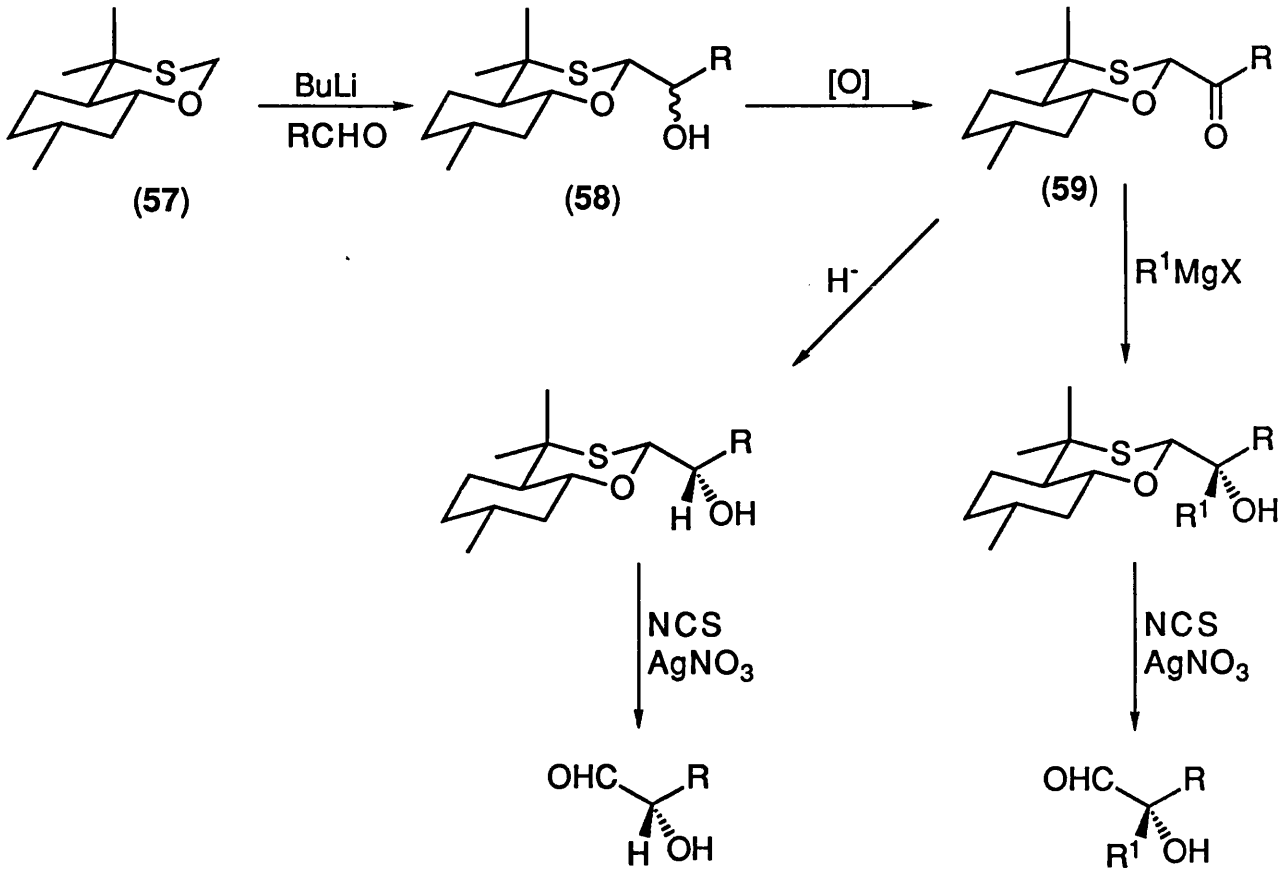
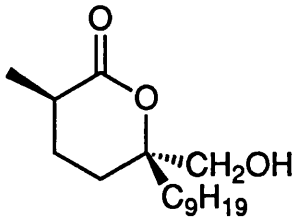


Figure 34

Addition to aldehydes gave mixtures of diastereomers, (**58**). These were oxidized to the ketone (**59**). Face selective reduction with (S)-alpine borane gave predominantely one diastereomer (92% d.e.). The other diastereomer (in 97% d.e.)was accessible by reduction with K-selectride. Chelation controlled addition of Grignard reagents afforded the tertiary alcohols with approaching 100% selectivity in some cases. This methdology has been applied to the asymmetric synthesis of the antibiotic malyngolide (**60**)[42].

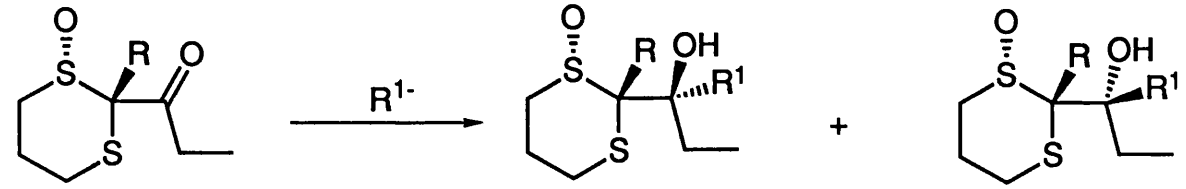


(60)

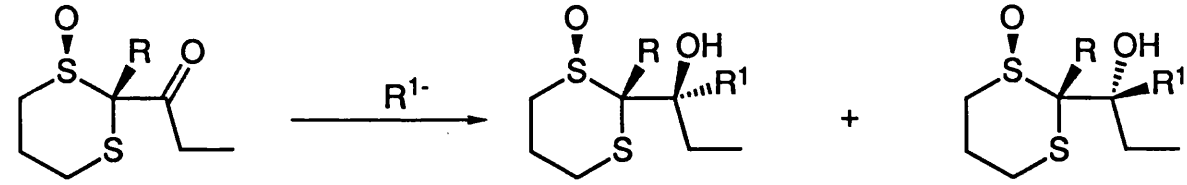
Figure 35

A more recent communication from Utimoto *et al.*[43] details the use of lanthanide trichloride mediated additions of organolithium and organomagnesium reagents to the acyl oxathiane (**59**). This led to the formation of the other diastereomer to that favoured in the Grignard additions by Eliel.

Page has employed similar methodology in the use of 2-acyl-1,3-dithiane-1-oxides[44].



Syn (**61**)



Anti (**62**)

Figure 36

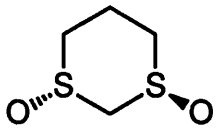
Both the *syn* (**61**) and *anti* (**62**) 2-alkyl-2-acyl-1,3-dithiane-1-oxides have been reacted with methyl magnesium iodide[44a], (R^1=Me) and reduced[44b] (R^1=H). The *syn* substrate gave exclusively a single diastereomer on reaction with the Grignard reagent in THF at -78°C. Good selectivity was also achieved with the *anti* substrate (up to 88% d.e.). The reduction of the substrates with DIBAL gave a single distereomer in most cases. The addition of $ZnCl_2$ often reversed the selectivity during the reduction. This was dependent upon the nature of the 2-alkyl group.

Similar methodologies have been adopted for many of the sulphoxide stabilised carbonyl anion equivalents mentioned in section 1.2.1, specifically in the use of (R)-methyl-*p*-tolyl sulphoxide by Resnati[27,45], (-)-1-chlorobutyl-*p*-tolyl sulphoxide by Yamakawa[26], dinaphthodithiepine by De Lucchi[46] and *p*-tolyl *p*-tolylthiomethyl sulphoxide by

Guanti[47].The vinyl chiral carbonyl anion equivalent of Braun (see figure 24) has also been adapted in this way to overcome poor selectivities in the anion addition step[48].

1.5 *trans*-1,3-Dithiane-1,3-Dioxide, A Chiral Carbonyl Anion Equivalent?

It was proposed to investigate the potential of *trans*-1,3-dithiane-1,3-dioxide (**63**), as a chiral carbonyl anion equivalent.



(63)

Figure 37

One advantage this compound may have, over those examples discused in the previous section, is its symmetry[a].The use of C_2 symmetric reagents and auxiliaries in asymmetric synthesis has become more widespread in recent years[49]. On first inspection, it might appear that the introduction of a symmetry element within a chiral auxiliary would be antithetical to the objective of achieving asymmetric induction in a chemical transformation. Enantiofacial differentiation, needed to provide asymmetric induction, requires only that the auxiliary lacks mirror or inversion symmetry and therefore, need not be asymmetric, only dissymmetric[b]. Although *trans*-1,3-dithiane-1,3-dioxide (**63**), is not strictly C_2 symmetric, since in the ground state the two faces of the molecule are not the same, C_2 symmetry is achieved by virtue of the fact that inversion of the ring produces a conformer identical to the first, figure 38.

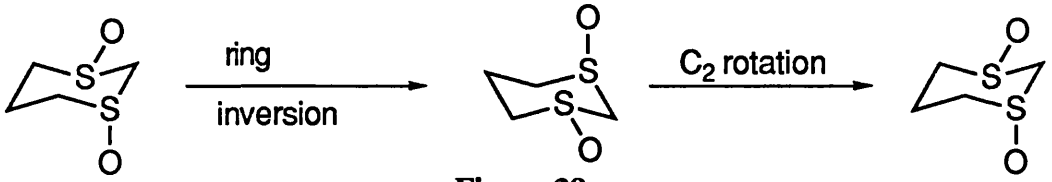


Figure 38

---

[a] The similarly symmetric disulphoxide employed by Solladie[28] was reported after this project was commenced.

[b] Asymmetric objects, by definition, are devoid of symmetry, dissymmetry applies to those lacking mirror symmetry[50].

Therefore, in solution where rapid inversion occurs both faces of the molecule will be equivalent. The presence of a C_2 symmetry axis serves the important function of reducing the number of possible competing diastereomeric transition states. Upon addition to prochiral electrophiles, a new chiral centre will not be created at C-2 and only two diastereomeric products are possible, figure 39, rather than four, which would be the case with a non C_2 symmetric species.

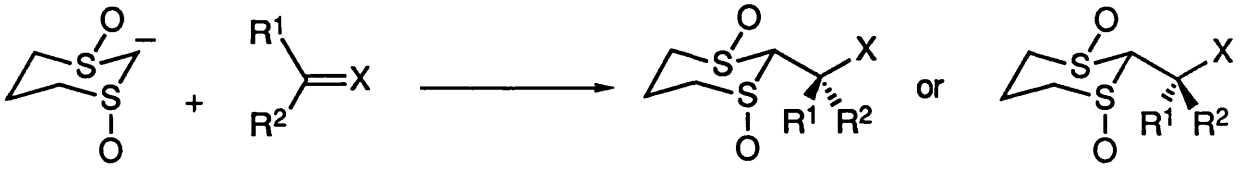


Figure 39

The study of the diastereoselectivity of (**63**) and initial studies into the hydrolysis of adducts, have been carried out with racemic material. This is justifiable as any selectivity shown by the racemate towards one diastereomer should be reflected in the production of the corresponding enantiomerically pure isomer when using homochiral material. As part of a separate project within the group, the asymmetric synthesis of (**63**) has been achieved[51]. This optically pure material has been used to check hydrolysis protocol for racemization (chapter 5). The synthesis of racemic (**63**), its reactions with aldehydes and imines, and the hydrolysis of the resultant adducts are discussed in the following chapters of this thesis.

CHAPTER 2. PREPARATION OF *TRANS*-1,3-DITHIANE-1,3-DIOXIDE.

2.1 Introduction.

At the outset of this project there was no literature procedure for the preparation of the *trans* dioxide (**63**). The mono oxide (**65**)[21b], the 1,1-dioxide (**66**)[52] and the tetraoxide (**68**)[53] were all known, and have been well characterized. The *cis* dioxide (**64**) was also known[52,54], but its highfield NMR spectrum has not been published in detail.

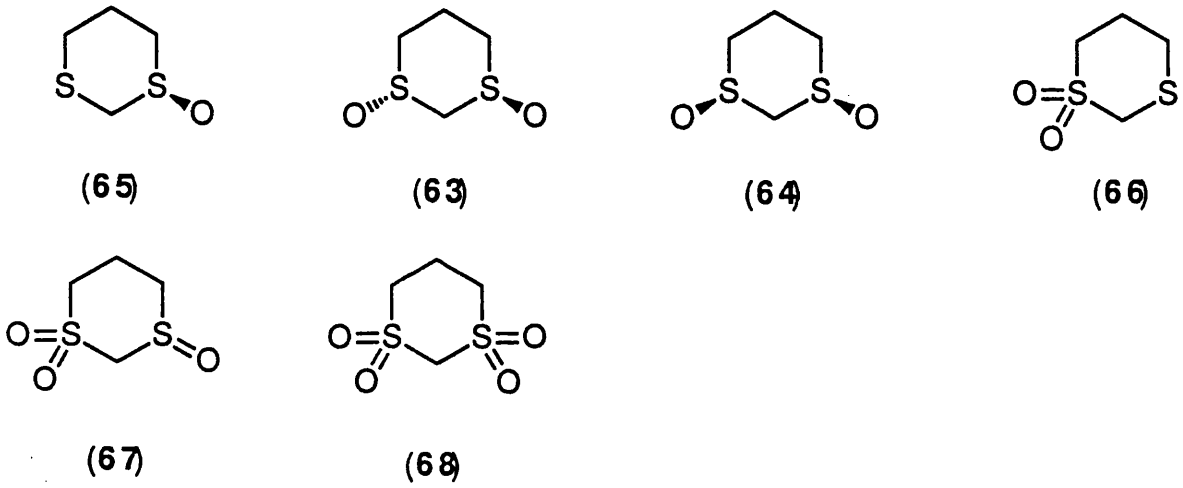
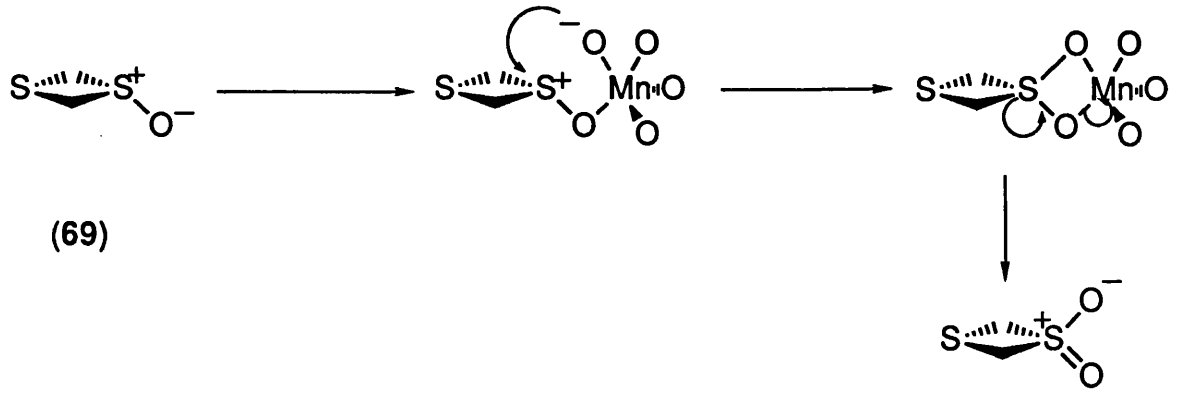


Figure 40

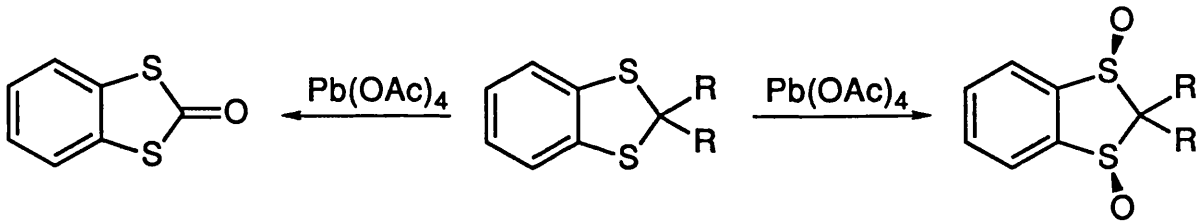
There are many examples in the literature of reagents that have been used to oxidise cyclic sulphides to the corresponding sulphoxides. Carey has investigated the oxidation of 1,3-dithiane. With MCPBA a mixture of the *cis* (**64**) and *trans* (**63**) isomers was obtained. However, the relative proportions of each was not ascertained, and only the *cis* dioxide (**64**) was isolated, in low yield (16%). Potassium permanganate gave exclusively 1,3-dithiane-1,1-dioxide (**66**), in preference to either of the bis sulphoxides. This type of reactivity has been observed by Block[55] in the corresponding four membered ring system, and was believed to be the result of chelation of the intermediate mono oxide (**69**), to the permanganate ion, figure 41.



(69)

Figure 41

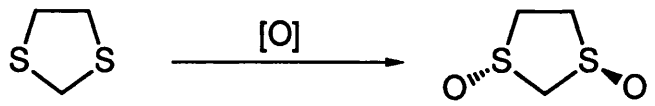
Lead tetraacetate has been used to oxidise benzodithioles[56] (**70**). The *cis*-1,3-dioxides (**71**) were obtained when the substrate was 2,2-disubstituted (R = alkyl or aryl). However unsubstituted examples were oxidised at carbon, to give (**72**).



(72) (70) (71)

Figure 42

Both MCPBA and sodium periodate have been used to prepare *trans*-1,3-dithiolan-1,3-dioxide, (**73**)[57]. The *trans* isomer was formed exclusively with both oxidants



(73)

Figure 43

The oxidation of 1,3-dithiane has previously been studied by other workers within the group[58,59,60]. Several oxidants; MCPBA, ozone, tetrabutylammonium periodate, hydrogen peroxide and sodium periodate were tried. MCPBA gave slightly more of the *cis* dioxide (**64**) (40:60 *trans* : *cis* ratio), which could be isolated in 26% yield. Ozone favoured formation of the *trans* dioxide (80:20) over the *cis* isomer. Approximately 10% each of the mono oxide

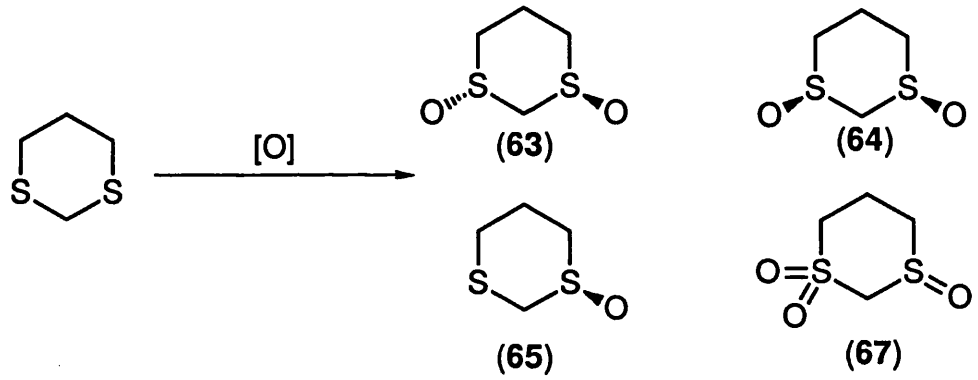
and the previously unknown trisoxide (**67**) were also produced with this reagent. Tetrabutyammonium periodate gave only the mono oxide (**65**). Hydrogen peroxide produced a mixture of the dioxides with a ratio of 80:20 *trans* to *cis*. The reagent of choice appeared to be sodium periodate and under these conditions the *trans* dioxide was formed predominantly (>95:5) and could be isolated in 60% yield[60a]. A significant amount of the trisoxide (**67**) was also produced in this reaction. Since these initial studies on the formation of *trans*-1,3-dithiane-1,3-dioxide (**63**) were carried out, the preparation of (**63**) has been reported by Bien[61]. Ozone, MCPBA and sodium periodate were used as oxidants. All three reagents were reported as showing preferential formation of the *trans* isomer. Reaction with ozone gave a 75:25 *trans* : *cis* ratio, which is similar to that obtained within the group. The reported selectivities for sodium periodate and MCPBA were however not as consistent. Bien reported a 65:35 ratio with MCPBA compared to 40:60. Sodium periodate was reported as giving a 70:30 ratio and not >95:5. Reaction temperature and solvent were different for the MCPBA oxidations and reaction time and work-up procedure differed with the periodate reactions. These differences could therefore account for the discrepancy between the two sets of results.

2.2 Synthesis of the Racemate.

On commencing work on this project, the current synthesis of (**63**) was not considered wholly satisfactory. Although the *trans* dioxide could be selectively produced, by periodate oxidation, isolation was problematic. Aqueous work-ups were not possible due to the highly polar nature of the dioxides, which are water soluble. Separation of periodate residues from crude reaction mixtures was therefore difficult. Extracting with methanol also dissolved inorganic material and extraction with chloroform failed to extract all the product. Separation of *cis* and *trans* isomers was also hard to achieve. Despite the *trans* isomer being the major product, recrystallization was not successful at removing the *cis* dioxide. The *cis* isomer is the more polar, and even when present at only 1% of the composition of dioxides it crystallized out along with the *trans* isomer. Separation could be achieved by careful column chromatography, although mixed fractions were always obtained.

It was proposed to investigate other oxidants in the hope of improving work-up procedures. A high selectivity in favour of the *trans* isomer is required due to the problems in separating the two dioxides. In the light of the variable results found previously by this group of the ratio of *trans* : *cis* dioxides formed by sodium periodate and the inconsistency with the recent literature report by Bien[61], it was also decided to further investigate the periodate oxidation of 1,3-dithiane.

Many of the reagents commonly used for the oxidation of sulphides to sulphoxides have already been studied. There have been recent reports on the oxidation of cyclic sulphides with sodium perborate[62] and OXONE[63]. These two reagents were investigated in the oxidation of 1,3-dithiane, the results are shown in table 1.



Oxidant	Conditions	mono oxide (65)	*trans*-dioxide (63)	*cis*-dioxide (64)	trisoxide (67)
OXONE	Acetone/H_2O 0°C 15 min	_	66	34	trace
$NaBO_3$	CH_3CO_2H 55°C 3 hrs	20	49	31	_
$NaBO_3$	MeOH/H_2O 55°C 2 days	14	39	27	20

Ratios were determined by NMR analysis of the crude reaction mixtures.

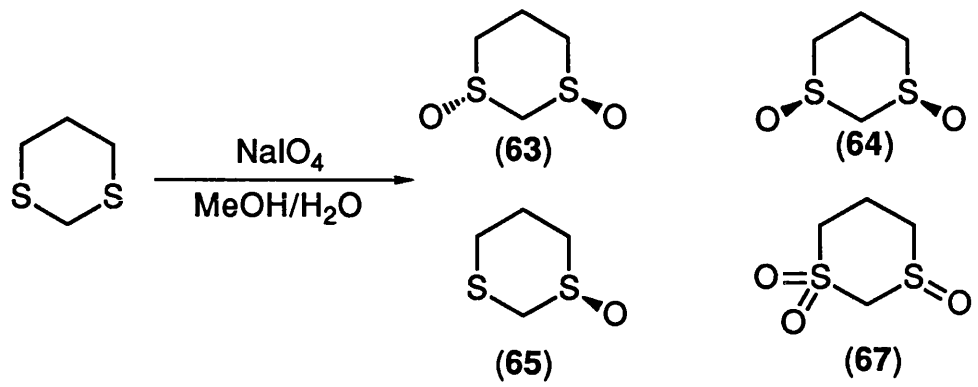
Table 1

Reaction with OXONE proceeded rapidly giving the dioxides with little contamination from the mono or tris oxides. The *trans* isomer was the major product but selectivity was moderate. Sodium perborate also gave the *trans* dioxide as the major product, but with reduced selectivity. The perborate oxidation in methanol/water was much slower than that in acetic acid. The formation of the dioxides was also less selective, with mono and tris oxides making up to 30% of the product composition. Neither of these reagents were considered a viable alternative to sodium periodate since the *trans* : *cis* ratios were worse and work-ups still required separation of large proportions of inorganic residues.

The sodium periodate oxidation of 1,3-dithiane was repeated several times. The results from four runs are shown in table 2, along with the results previously obtained within the group.

No clear pattern is apparent from the product distributions, and no firm conclusions will be drawn. However entry 5 is significantly different from the others, with a much higher ratio of the *trans* dioxide relative to the *cis* isomer. There was also a much larger proportion of the tris oxide from this reaction. It could therefore be concluded that the differences in the *trans* : *cis* ratios are dependent upon the amount of over oxidation that has occurred. If the *cis* dioxide is oxidised to the tris oxide at a faster rate than the *trans* isomer then this could account for the results obtained.

A slightly improved work-up procedure was developed for the sodium periodate oxidation. Previously, reaction solvents were evaporated and the residue extracted several times with methanol. However, inorganic residues were also brought through by this method which reduced the efficiency of subsequent column chromatography. Filtration of the crude reaction residue through a short one inch pad of silica gel, eluting with acetone gave almost quantitative yields of the dioxides, with no inorganic contaminants. As a result of these improvements to the work-up procedure, sodium periodate remains the reagent of choice for the synthesis of *trans*-1,3-dithiane-1,3-dioxide.



Entry	mono oxide (65)	*trans*-dioxide (63)		*cis*-dioxide (64)	trisoxide (67)
			trans	*cis*	
1	22	62	90	7 10	9
2	-	82	91	8 9	10
3	-	75	80	19 20	6
4	6	74	84	14 16	6
5*	-	71	>95	trace 5	29

* Result from previous work[58,60a].

Table 2

The factors that control sulphoxide configuration in the oxidation of cyclic sulphides, by different oxidising agents has been the topic of a paper by Johnson[64]. Some of the arguments put forward by Johnson can be used to rationalise the results obtained in the oxidation of 1,3-dithiane. It appeared that "steric approach control" prevails in oxidations with peroxy reagents such as MCPBA, where product distribution was controlled by competitive attack of the sulphide lone pair from the sterically favoured *vs.* the hindered side. The configuration of

1,3-dithiane dioxide is determined during the second oxidation step from the mono oxide (**65**). In solution (**65**) has been shown to exist in two conformations[52]. The minor conformer has the oxygen axial. MCPBA oxidation at the sterically less hindered equatorial site will give the *trans* dioxide from this conformer, figure 44.

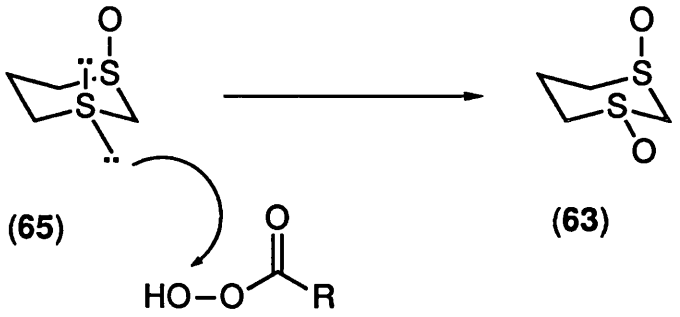


Figure 44

The major conformer of (**65**) has the oxygen equatorial. MCPBA oxidation of this conformer at the least hindered position will give the *cis* dioxide, figure 45.

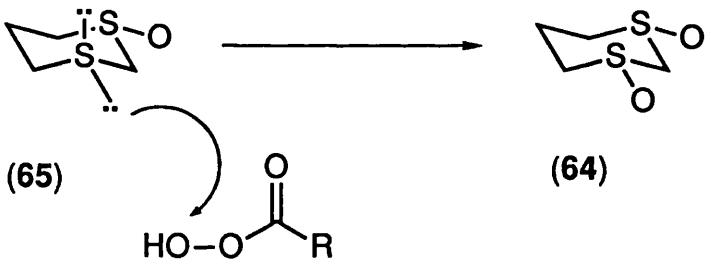


Figure 45

MCPBA was found to give slightly more of the *cis* dioxide, the product distribution probably mirrors the relative proportions of equatorial and axial conformers adopted by the mono oxide.

The oxidation of sulphides by sodium periodate may be described in terms of a cyclic mechanism, figure 46.

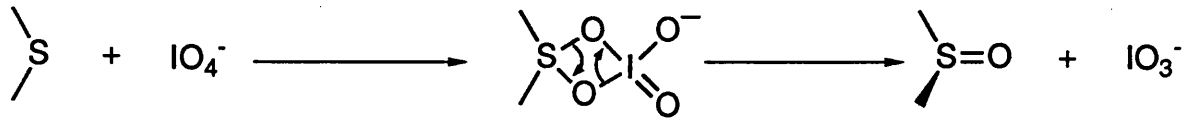


Figure 46

Johnson proposed that the stereochemistry of the oxidation process is under "product development control." That is to say, the factors influencing the stability of the final products are operative in the transition state. Therefore the more stable isomer is that which is favoured. It should be noted that this is not the same as "thermodynamic product control" where-by any initially formed products are equilibrated under the reaction conditions. Neither periodate nor iodate isomerize sulphoxides. The sodium periodate oxidation of 1,3-dithiane gives a greater proportion of the *trans* dioxide, which would suggest that this is the more stable dioxide isomer. This has been proven to be the case. Equilibration studies with N_2O_4 performed within the group[59,60b], show that both pure *cis* and pure *trans* samples of the dioxides can be equilibrated to give a similar equilibrium ratio of the isomers of approximately 85:15 in favour of the *trans* dioxide. The greater thermodynamic stability of the *trans* isomer has been confirmed by molecular mechanics calculations[c].The *trans* isomer was 0.8 Kcalmol^{-1} more stable than the *cis*. The enhanced stability of the *trans* isomer is thought to arise from a favourable dipole-dipole interaction between the two sulphoxide groups and evidence for this effect is found in the

X-ray crystallographic analysis of (**63**), figure 47, which reveals a distortion of the axial sulphinyl oxygen towards the equatorial sulphoxide.

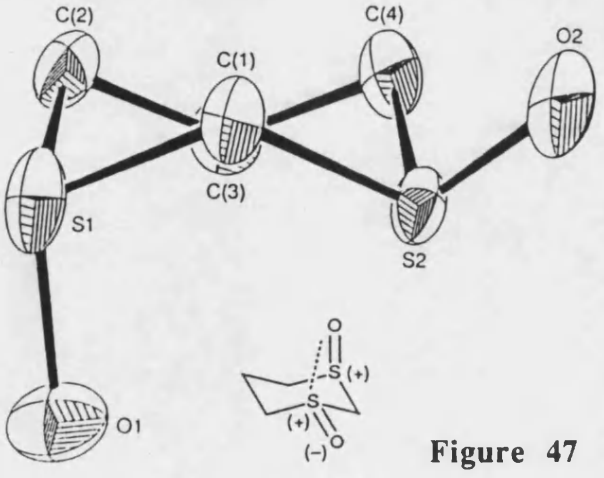


Figure 47

[c] We are indebted to P. Osgerthorpe, University of Bath molecular graphics suite, for performing the calculations. Values for the sulphoxide parameters were taken from a report by Allinger[65].

In summary, racemic *trans*-1,3-dithiane-1,3-dioxide (**63**) can be prepared by selective oxidation of 1,3-dithiane with sodium periodate to give the more stable dioxide isomer. Work-up and purification remain awkward, but the procedure has been used routinely on scales up to 40g.

2.3 Synthesis of Homochiral *trans*-1,3-Dithiane-1,3-dioxide.

The asymmetric synthesis of homochiral *trans*-1,3-dithiane-1,3-dioxide (**63**) has been accomplished as part of a separate project within the group[51].

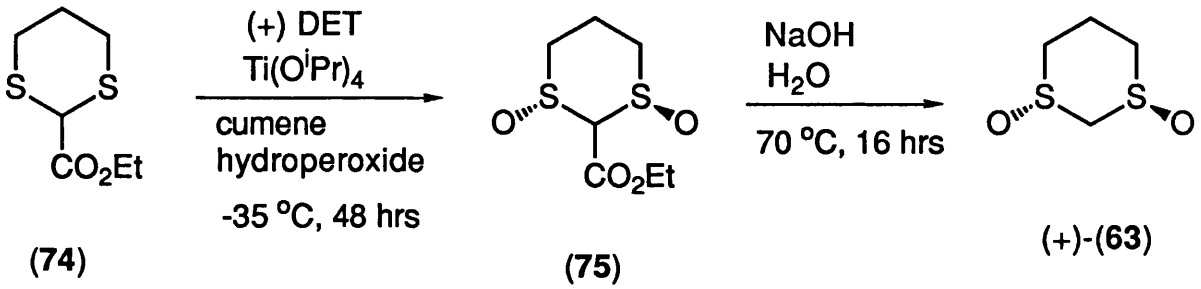


Figure 48

Using conditions that have been employed by Modena[66] for the asymmetric oxidation of sulphides, 1,3-dithiane-2-ethyl carboxylate (**74**), was oxidised to the *trans* dioxide (**75**) in very high enantiomeric excess (>97% e.e.). Decarboxylation of the carboethoxy group (initially required to co-ordinate to the chiral metal oxidising complex) gives (+)-(**63**). After one recrystallization material with >99.8% e.e., as estimated by chiral shift NMR, was obtained. The absolute stereochemistry of (+)-(**63**) has been assigned (1R,3R)[51].

Most of the studies described in the following chapters have been carried out with racemic (**63**). The homochiral material has been used to check for racemization during hydrolysis procedures.

CHAPTER 3. ADDITIONS TO ALDEHYDES.

3.1 Introduction and Previous Work.

The addition of carbanions of 1,3-dithiane and α-sulphoxide stabilised carbanions to carbonyl compounds is well established and has been thoroughly reviewed[67,68]. Reactions of carbanions stabilised by two sulphoxides are however, virtually unknown. Apart from the reactions carried out by this group (with *trans*-1,3-dithiane dioxide, 5,5-disubstituted *trans*-1,3-dithiane dioxides, *trans*-1,3-dithiolane dioxide and *trans*-1,3-benzadithiole dioxide) the only examples of which we are aware are the reactions of lithiated bis-*p*-tolylsulphinylmethane which have been recently published by Solladie[28], (see chapter 1, figure 23).

The presence of two sulphoxides dramatically increases the acidity of the α-protons. This can be seen from the pKa of *trans*-dithiane dioxide, (**63**) which has been measured, and found to be 25.0, in DMSO[69]. This is considerably different from single sulphoxides, (pKa's around 35) and from 1,3-dithiane (pKa = 39). As a consequence a greater variety of bases can be used to form the anion of (**63**). The greater stability of the disulphoxide stabilised anion may however reduce its nucleophilicity as compared to these other carbanions.

Other workers within the group have previously studied the anion reactions of (**63**) with aldehydes[58,60,71]. A problem encountered during this work was the solubility of (**63**). The *bis*-sulphoxide is highly polar and dissolves readily in water. It can be dissolved in acetonitrile, DMF, DMSO, pyridine, ethanol and methanol by gentle heating. It cannot, however be dissolved in organic solvents that are commonly used for anion reactions, (diethyl ether, THF or hexane). Attempted alkylation of (**63**), as a suspension in THF, by treatment with LDA followed by methyliodide, proved unsuccessful. Alkylations could however be carried out in DMF and in DMSO with NaH as the base, and in pyridine/THF mixtures with LDA. Pyridine/THF mixtures were found to be the most suitable for performing anion reactions with aldehydes. Butyllithium was found to be the most convenient base to use. One of the advantages of using butyllithium is that, when using pyridine as solvent, the base may be titrated into the reaction mixture, since upon addition of greater than one equivalent a yellow colour persists. It is known that ^{n}butyllithium adds to pyridine to give the highly

coloured adduct (**76**)[72], and presumably this acts as the base to deprotonate the dithiane dioxide (**63**), figure 49.

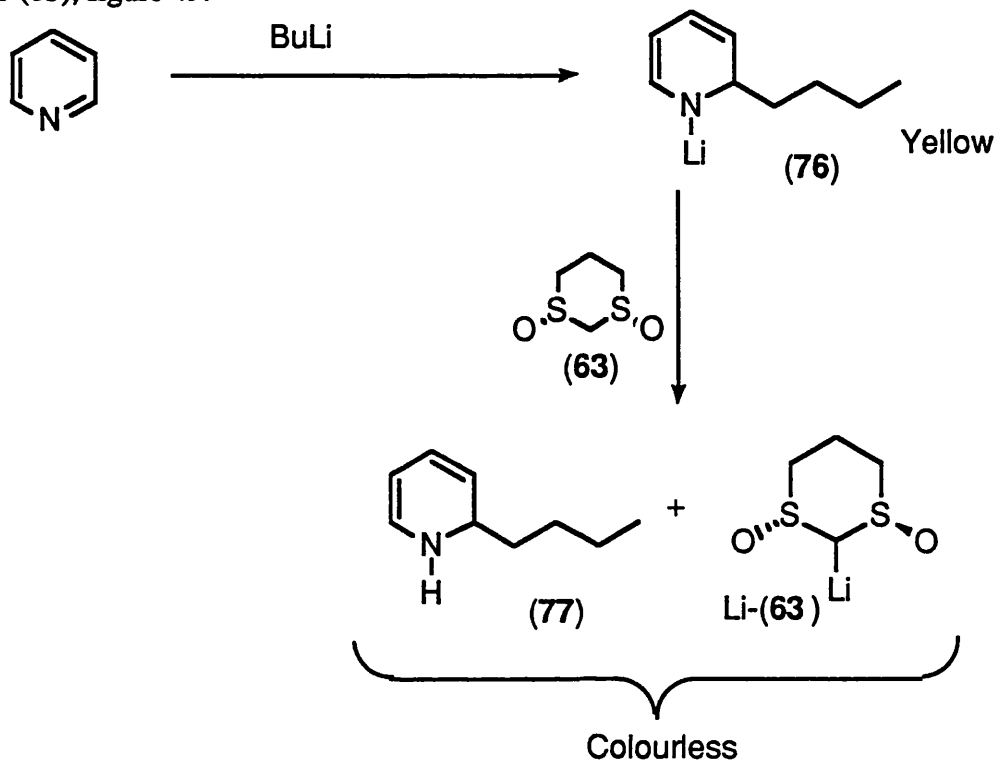


Figure 49

Lithiated (**63**) and the dihydropyridine adduct (**77**), are colourless, therefore once all of (**63**) has been deprotonated, the endpoint of the titration is indicated by a permanent yellow colour from the butyllithium-pyridine adduct (**76**). Reactions were carried out with four aldehydes, valeraldehyde, isobutyraldehyde, pivalaldehyde and benzaldehyde (R = ^{n}Bu, ^{i}Pr, ^{t}Bu and Ph, figure 50), at both 0 °C and -78 °C.

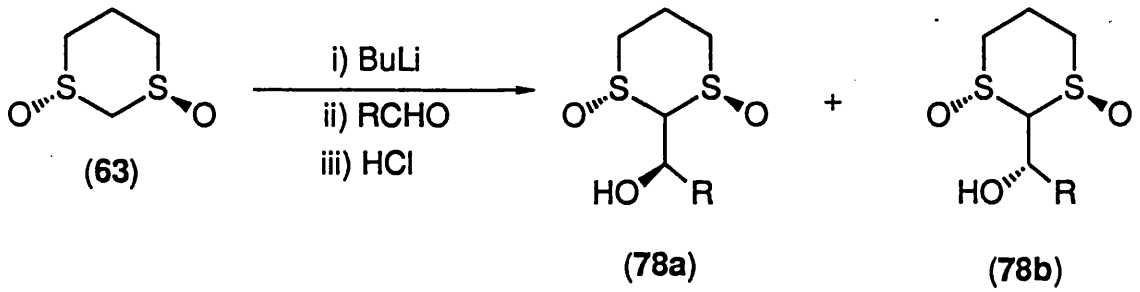


Figure 50

At -78 °C the reactions were under kinetic control and the product distribution did not vary with time. A single diastereomer of the products (*i.e.* pure (**78a**) or pure (**78b**)) could be resubjected to the reaction conditions and be recovered unchanged. The selectivities at this

temperature were poor, ranging from 1:1 to 2:1. At 0 °C the reactions with pivalaldehyde and benzaldehyde were under thermodynamic control. Equilibration of the isomers occurred and if either of the diastereomeric products were resubjected to the reaction conditions the same ratio of compounds was produced. The selectivities were better when equilibration occurred and ratios of up to 1:6 were obtained, depending on the aldehyde used. One problem found with these reactions was that over prolonged periods of time at 0 °C, elimination of the adducts occurred under the reaction conditions. This prevented true equilibration ratios from being obtained. Reactions with isobutyraldehyde and valeraldehyde did not equilibrate at 0 °C and gave similar ratios of products to those obtained at -78 °C.

An important observation to have been made during these initial studies was that the method of quenching the reaction had a dramatic effect upon the yield of the reaction. This observation is rationalised below.

An equilibrium exists between the adduct alkoxides and lithiated (**63**), figure 51.

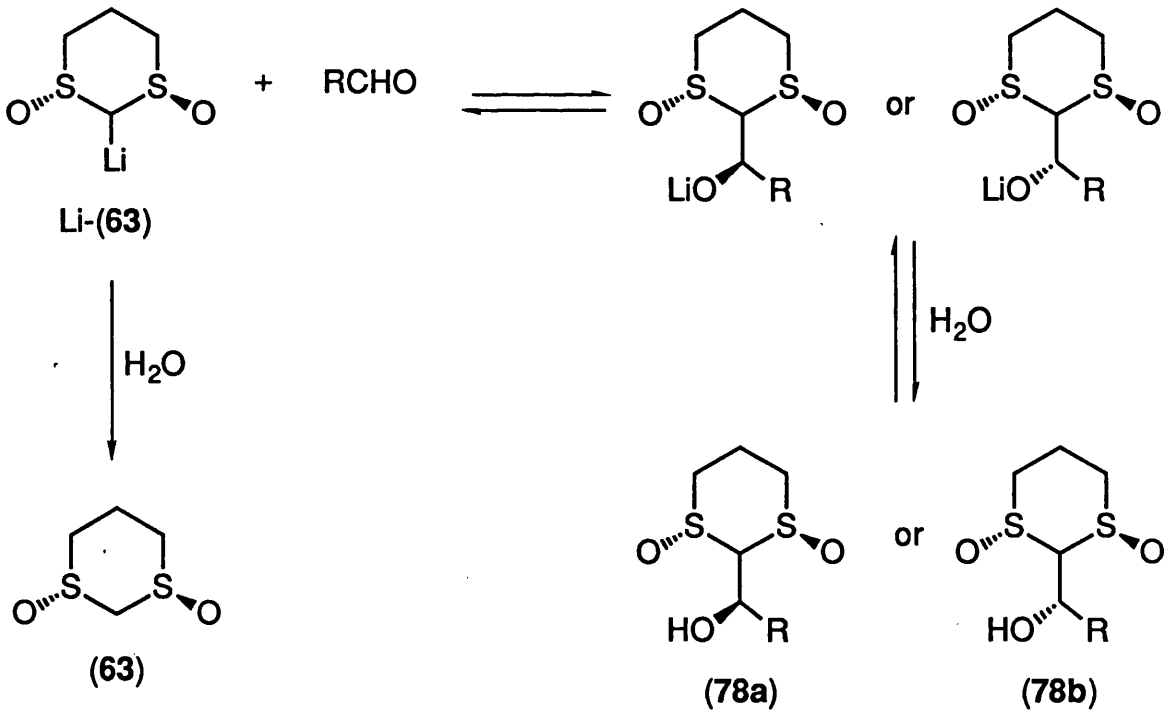
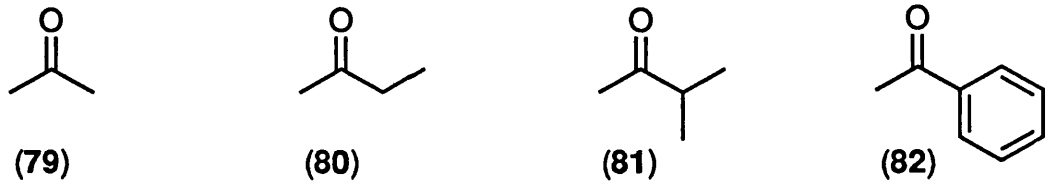


Figure 51

Addition of water quenches the alkoxides slowly but reversibly and allows quenching of the more basic substrate, lithiated (**63**). Since the initial quench with water is reversible the ultimate product is (**63**). Even quenching with aqueous NH_4Cl resulted in the return of

substantial amounts of (**63**) showing that the rate of quenching the reaction was important. A more rapid acid quench was found to quench the reaction irreversibly and favouring the right hand side to give predominantly the adducts, (**78**), with little starting material.
The continuation of this work, with the aim of increasing and optimising the anion reactions of *trans*-1,3-dithiane dioxide (**63**) with aldehydes is described in the following sections of this chapter.

A separate, parallel study was carried out within the group to investigate the reactions of (**63**) with ketones[73]. In summary, the conclusion from this work was that only sterically unhindered aliphatic ketones will react with dithiane dioxide. Adducts could be obtained with acetone (**79**) and methyl ethyl ketone (**80**), although in low yield. However, if the ketone had any α-branching or was resonance stabilised, no reaction occurred and adducts could not be obtained with methyl isopropyl ketone (**81**) or acetophenone (**82**), despite many attempts.



(**79**) (**80**) (**81**) (**82**)

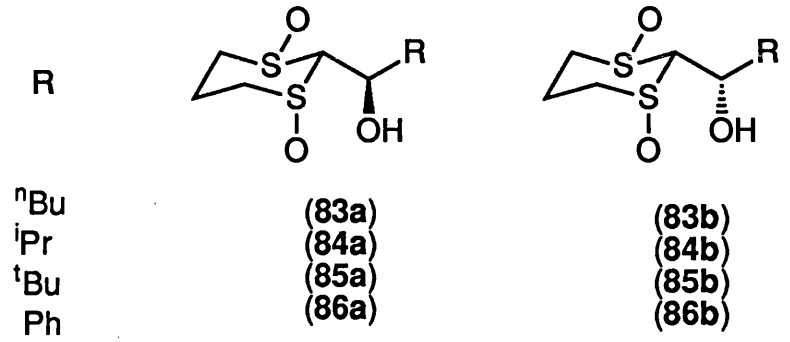
Figure 52

The failure to obtain adducts with most ketones can be attributed to the high stability of carbanions of dithiane dioxide. Compared with alkyllithium or Grignard reagents (pKa typically 40-50) the pKa of (**63**) is much lower (25.0[69]) and hence (**63**) is less reactive. The increase in steric crowding of α-branched ketones or the increase in stability due to conjugation of aromatic ketones are sufficient to prevent reaction.

3.2 Results and Discussion.

Reactions of (**63**) with aldehydes fall into two distinct classes; those at 0 °C, which are under thermodynamic control, where the products equilibrate, and those at low temperature (-40 to -78 °C) which are under kinetic control. Certain conditions were varied for both types of reactions in order to try and increase stereoselectivities. The conditions that were varied and the effect this had on the selectivity are described and discussed below.

The ratios of diastereomers formed were measured by HPLC and, to a lesser extent, NMR analysis of crude reaction mixtures. Aliquots could be taken out at various time intervals to give an indication of how product distribution varied with time. The adducts with valeraldehyde, isopropylaldehyde, pivalaldehyde and benzaldehyde have all been prepared under established conditions and fully characterised.



R		
^{n}Bu	**(83a)**	**(83b)**
^{i}Pr	**(84a)**	**(84b)**
^{t}Bu	**(85a)**	**(85b)**
Ph	**(86a)**	**(86b)**

Figure 53

X-ray structures have been obtained for the pivalaldehyde adduct (**85a**) and both of the benzaldehyde adducts (**86a**) and (**86b**). The assignment of the relative stereochemistry of all other adducts has been based on comparison with these compounds in terms of tlc and HPLC behaviour and ^{1}H and ^{13}C NMR spectra.

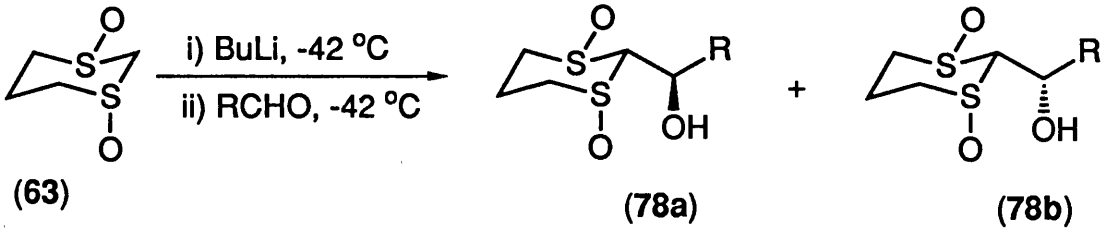
3.2.1 Temperature of Formation of the Anion.

It has been found that the stereoselectivity in kinetically controlled reactions of sulphoxide stabilised carbanions can be dramatically influenced by the temperature of formation of the anion since at higher temperatures reorganization of the lithium species can occur, giving a chelated anion[74]. This effect was investigated with dithiane dioxide. The butyllithium derived anion of (**63**) was formed at both 0 °C and -45 °C and then reacted with pivalaldehyde at -78 °C. However the product distribution was very similar in both cases at around a 1:1 ratio. In all future experiments with butyllithium anion formation was carried out at the temperature of reaction with the aldehyde.

3.2.2 Variation of Solvent.

The effect of changes to the pyridine/THF ratio upon the stereoselectivity of the reaction was investigated, under conditions of both kinetic and thermodynamic control.

Since pyridine freezes at -42 °C, if the reaction is to be carried out in the absence of THF this places a limit on the minimum temperature possible. Therefore, all reactions under kinetic control were carried out at -42 °C, (achieved by using a pyridine/CO_2 bath). Samples were removed, and analysed by HPLC, over a period of time to ensure that equilibration was not occurring at this temperature. Therefore using the established conditions for generation and reaction of the anion of (63)[71], the reaction was carried out in pyridine/THF (1.6 : 1) and in neat pyridine, at -42 °C, figure 54.

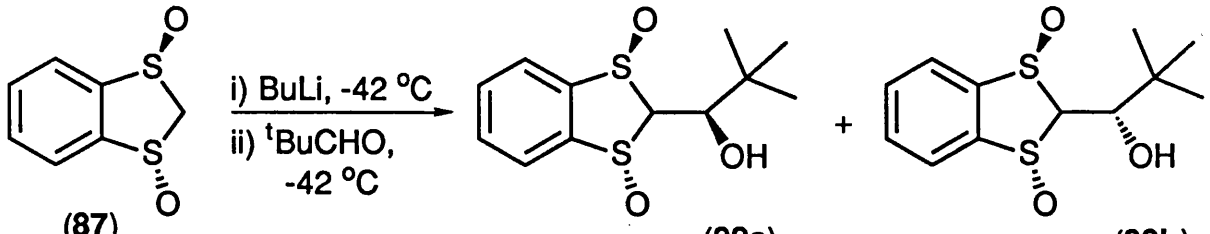


(63) (78a) (78b)

Figure 54

Two different aldehydes were used, valeraldehyde (R = ^{n}Bu) and pivalaldehyde (R = ^{t}Bu). In both cases, the ratio of products was found to be almost identical, with and without THF present, at around 2:1.

In order to investigate the reaction in the absence of pyridine a slightly different system was used. *trans*-1,3-Dithiane dioxide (63) is not soluble in THF, while, *trans*-benzodithiole-1,3-dioxide (87) is, figure 55. This C_2 symmetric molecule has been prepared as part of a different project within the group[75] and was used to investigate anion reactions with aldehydes in the absence of pyridine.



(87) (88a) (88b)

Figure 55

The above reaction was carried out in pyridine/THF (1.6 : 1), neat pyridine and neat THF. In the reactions performed in pyridine, it is the lithiated dihydropyridine (76), (figure 49) that is

acting as the base. To be consistent, one equivalent of pyridine was added to the reaction carried out in "neat THF," to allow formation of (**76**). Therefore, any change in selectivity can be attributed to the change of solvent rather than to a change of the base used. In all cases the product distribution was found to be similar at around a 1:1 ratio (**88a**) to (**88b**).

The effect of changing pyridine/THF ratios was also investigated under conditions of thermodynamic control. The butyllithium derived anion of (**63**) was reacted with pivalaldehyde at 0 °C and the reaction monitored over a period of time. The reaction was carried out in pyridine/THF (1.6 : 1) and in neat pyridine , similar selectivities were observed for both reactions with one isomer being increasingly favoured, up to a ratio of around 5:1, as equilibration of the isomers occurred.

It was concluded from these experiments that pyridine/THF ratios or the complete absence of either pyridine or THF had little or no effect upon the selectivity of the reaction under conditions of either thermodynamic or kinetic control.

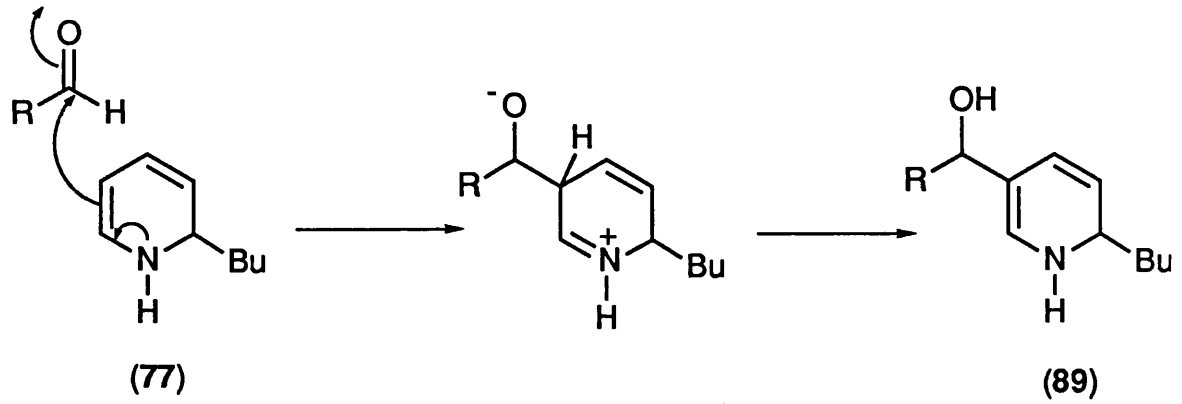
At a much later stage in the project, reactions were tried in DMF under a variety of conditions. In all cases, the selectivity was the same as reactions performed in pyridine/THF. Due to the difficulties in removing DMF on work-up, this was not considered a good alternative.

Since the absence of THF had no effect upon selectivity, some reactions at 0 °C were carried out in neat pyridine. However when using NaHMDS as base (see next section, 3.2.3), reaction yields were diminished. Pyridine/THF (1.6 : 1) remains the solvent system of choice for anion reactions with aldehydes.

A worrying trend emerged from the reactions carried out under thermodynamic conditions, at 0 °C. It appeared that as time progressed an increasing amount of starting material was

present in the reaction mixtures, until over prolonged periods there was essentially only starting material left [d].

Therefore, the question arose as to how and why starting material was being returned. It was suspected that the dihydropyridine (**77**) produced from the reaction of butyllithium and pyridine, figure 49, could be the cause. There is some literature precedent for the reaction of dihydropyridines and lithiated dihydropyridines with carbonyl compounds[76,77]. One can envisage the dihydropyridine (**77**) reacting with an aldehyde, figure 56, to give the adduct (**89**).



(**77**) (**89**)

Figure 56

This is similar to the reaction observed for (**77**) with isocyanates[76]. Alternatively the dihydropyridine, (**77**) could reduce the aldehyde to give the aromatized pyridine, (**90**) and the alcohol, figure 57. A similar reaction has been observed between lithiated (**77**) and benzophenone[77a].

---

[d] In previous work[58,60a,71], it was not possible to monitor the amount of starting material present in the crude reaction mixture, due to by-product peaks on the HPLC traces. Changes in the way that the HPLC samples are treated (see experimental section) has meant this is now possible.

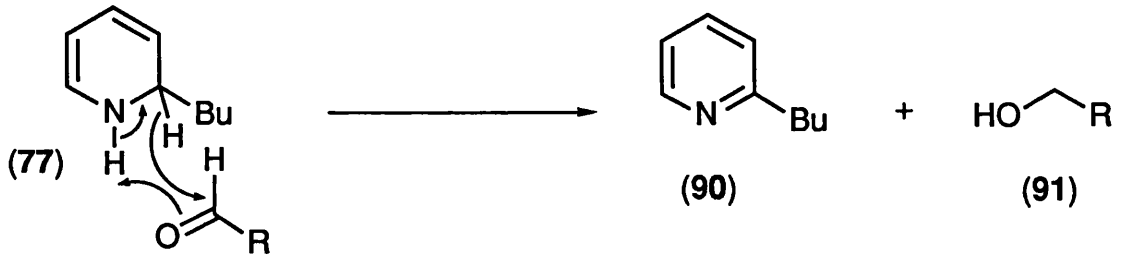


Figure 57

In both of the above cases an alcohol is produced . This might provide a proton source which could act as a slow quench in the anion reactions, which would account for the return of starting material.

To test these hypotheses the dihydropyridine (**77**) was reacted with pivalaldehyde. None of the reduced alcohol (**91**), figure 57, was detected. However a small amount of a compound, whose NMR spectrum is consistent with that expected for an adduct of the type (**89**), figure 56 (R = ^{t}Bu) was isolated. Attempts to purify and fully characterize this compound were unsuccessful. In anion reactions of (**63**) with butyllithium in pyridine, no adducts of the type (**89**) could be detected.

For reactions under thermodynamic control longer reaction times are required to achieve equilibrium of the adducts, and it was during these long reaction times that starting material was being returned. This problem may be preventing true equilibrium ratios from being obtained, so despite the lack of firm evidence that dihydropyridines were a problem, it was decided to investigate bases which do not react with pyridine.

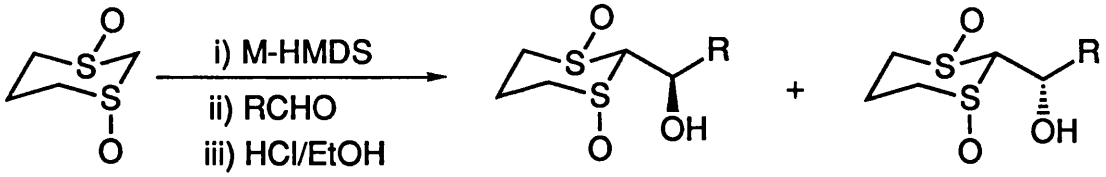
Reactions with other bases under kinetic and thermodynamic control are best considered separately.

3.2.3 Investigation of Thermodynamically Controlled Reactions.

In previous work only butyllithium and LDA have been used as bases in reactions of (**63**) with aldehydes. Sodium hydride has also been used but only in alkylation reactions.

To investigate the effect of counterion upon the selectivity of thermodynamically controlled reactions lithium, sodium and potassium hexamethyldisilazane bases were used in combination with the four aldehydes previously used. The results are summarised in table 3.

The selectivities varied considerably. A few general trends were apparent from these reactions. It can be seen that changing from lithium to sodium to potassium, results in increased quantities of eliminated material. The ratios shown in table 3 are those achieved before any significant elimination occurred, and they are probably not the true thermodynamic ratios of adducts particularly for potassium. Equilibration times were very different for different aldehydes or for different metals and range from a few minutes to several hours.



(63) (a) (b)

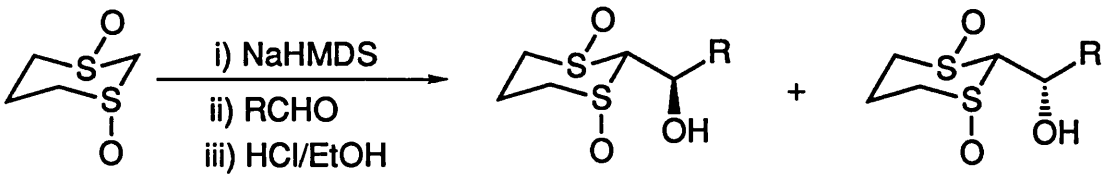
Product Ref^{n} N^{o}	R	Ratio of (a) : (b)		
		Li	Na	K
(83)	^{n}Bu	-	77 : 33	80 : 20
(84)	^{i}Pr	60 : 40	60 :40	70 : 30
(85)	^{t}Bu	82 : 18	40 :60	30 : 70
(86)	Ph	88 : 12	**96 : 4**	90 : 10

Table 3

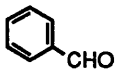
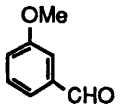
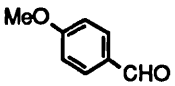
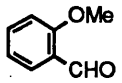
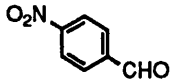
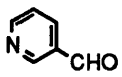
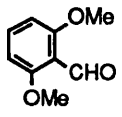
It is clear that the counterion used greatly affects the selectivity of the reaction. For example with LiHMDS and pivalaldehyde a selectivity of 82:18 was achieved, in favour of (**85a**). However, with KHMDS, a 30:70 ratio was observed, now in favour of (**86b**). The R group of the aldehyde used also had a profound affect on the selectivity. The reactions of NaHMDS

with pivalaldehyde and isobutyraldehyde gave very poor selectivities whereas with benzaldehyde a 96:4 ratio was obtained.

Some reactions with sodium hydride and potassium hydride were also carried out. Selectivities were very similar to those obtained with NaHMDS and KHMDS respectively. This reinforces the conclusion that it is the nature of the counterion that is important in determining the ratio of adducts obtained. Solutions of the HMDS bases are commercially available, and being much easier to dispense and handle than the hydrides, they are therefore the preferred reagents. In order to rationalise these results, attention was focused on the benzaldehyde/NaHMDS combination, where a much higher selectivity was achieved, compared to most of the other reactions. A number of different aromatic aldehydes were tried, with NaHMDS as the base in each case. The results are shown in table 4[78]. Initially, reactions were performed on very small scale and monitored by HPLC over a period of time. The ratios in table 4 are those obtained before significant elimination occurred. The rate of elimination varied, depending on the aldehyde, and was not particularly rapid with any of these aldehydes. Having determined the best reaction time from the HPLC monitored reaction, preparative reactions were then performed to obtain yields and to isolate the products for characterisation. Only the major isomer (**a**) was isolated from entries 1-5. The adducts (**97**) from 2,6-dimethoxybenzaldehyde were not separable and were characterised as a mixture of diastereomers. The adducts from 3-pyridylcarboxaldehyde, (**96a**) and (**96b**) were obtained as their HCl salts, formed during the acidic quench of the anion reaction. It was not possible to purify or analyse the salts, and attempts to isolate the free base resulted in decomposition. Instead, treatment of the crude product from the anion reaction, with hexamethyldisilazane and trimethylsilylchloride produced the TMS ethers (**98a**) and (**98b**), figure 58. Analysis by NMR of the products from the silylation reaction gave the ratio shown in table 4. The TMS ethers could be separated and the major diastereomer (**98a**)was fully characterised.



(63) (a) (b)

Entry	Product Ref^n. N^o.	Aldehyde	Ratio (a) : (b)	Isolated yield of (a)	Equilibration time
1	(86)		96:4	87%	30 mins
2	(92)		95:5	64%	3 hrs
3	(93)		95:5	72%	3 hrs
4	(94)		95:5	76%	18 hrs
5	(95)		95:5	42%	5 hrs
6	(96)		97:3	71%[a]	30 mins
7	(97)		70:30	66%[b]	1 hr

a : Ratio and yield determined after derivatization of the alcohols to the TMS ethers (98).

b : Combined yield of isomers (a) and (b), which could not be separated.

Table 4

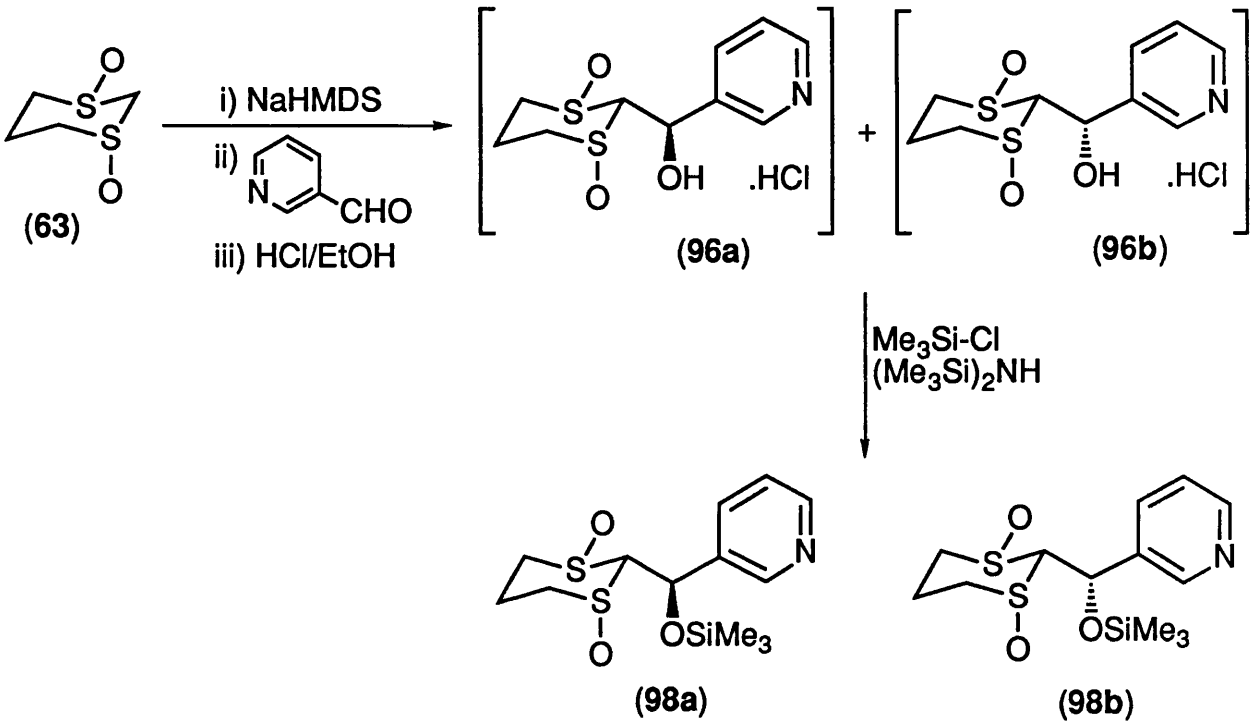


Figure 58

Good comparable selectivities were obtained for most of the examples in table 4. The only exception being the 2,6-dimethoxybenzaldehyde adducts (**97**), entry 7. These adducts were also unusual in that they could not be separated by column chromatography, all the other aromatic aldehyde adducts showed two distinct, well separated spots on tlc for the two diastereomers.

The rates of equilibration were very different. It would be reasonable to expect more reactive electron deficient aldehydes to equilibrate faster than those with electron donating groups. However changing from *p*-methoxybenzaldehyde to benzaldehyde to *p*-nitrobenzaldehyde does not result in a trend in equilibration time. Obviously more than one factor is contributing to the reaction rate and presumably the energy of the final product is also important in affecting the rates of equilibration.

A number of unsuccessful reactions with aromatic aldehydes and ketones were also carried out. Furfuraldehyde (**99**) was reacted with the sodium anion of (**63**) but HPLC traces showed only eliminated material present. Presumably the rapid elimination of the adducts of this

aldehyde is due to the participation of the oxygen lone pair, to give the conjugated product (**100**), figure 59.

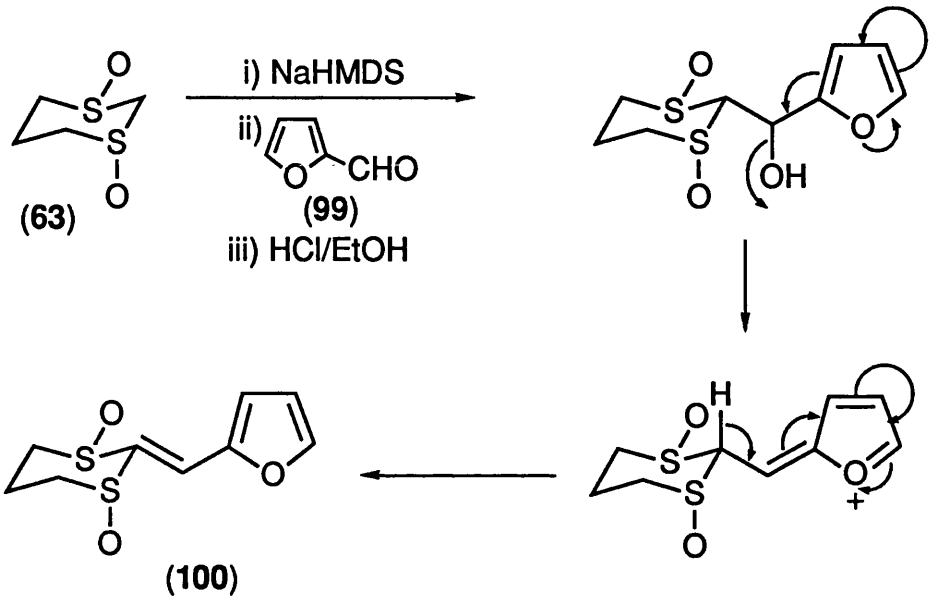


Figure 59

Reaction with phenethyl aldehyde (**101**) was carried out to investigate any effect from moving the aromatic group one carbon further away from and out of conjugation with the carbonyl, however no products were detected. The failure of this reaction is probably due to proton transfer from the acidic benzylic position of the aldehyde, figure 60.

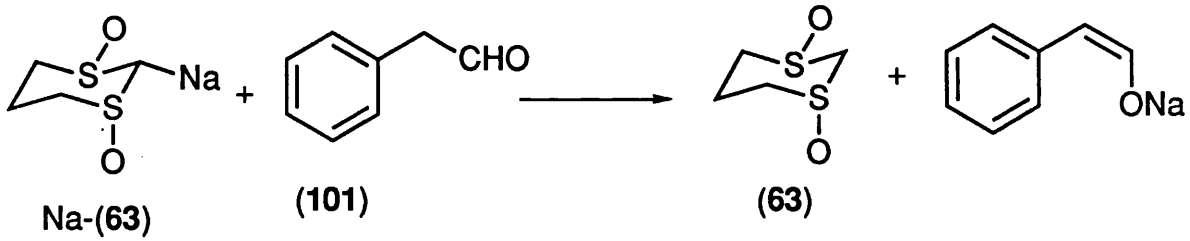
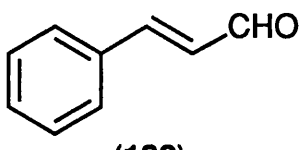


Figure 60

The conjugated aromatic aldehyde, cinnamaldehyde (**102**) was tried. Competing 1,2 and 1,4 addition gave a mixture of several products which could not be separated by HPLC.



(**102**)

Figure 61

The aromatic ketones acetophenone and the more reactive trifluoroacetophenone were added to Na-(**63**) but in each case no reaction occurred. It has subsequently been found that (**63**) does not react readily with ketones[73], and this observation is discussed in the introduction to this chapter.

The good selectivities obtained with aromatic aldehydes could be the result of a favourable interaction with the π-system of the aromatic ring. A similar interaction could also be possible with the π-system of an acetylene, and therefore the reaction with an acetylinic aldehyde was investigated. The aldehyde (**104**) was prepared from the commercially available alcohol (**103**) by Swern oxidation[79].

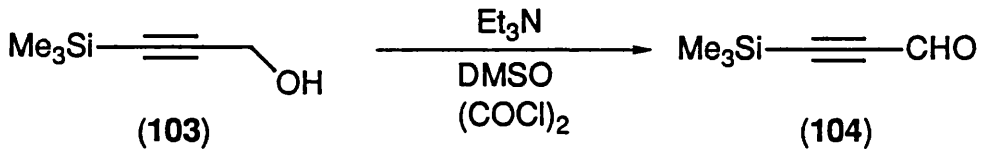


Figure 62

Reaction of (**104**) with Na-(**63**) at 0 °C resulted in decomposition of the aldehyde and no products were detected. The aldehyde (**104**) was reacted with Li-(**63**) at -78 °C and NMR analysis of the crude reaction product indicated a low yield (*ca.* 30%) of the adducts (**105**) in a 2:1 ratio. However, attempts to isolate pure samples resulted in decomposition.

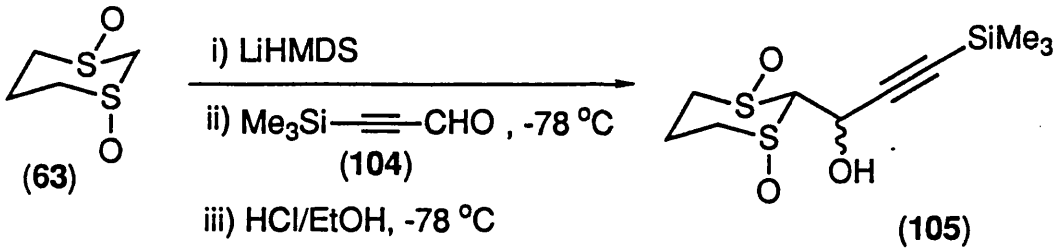
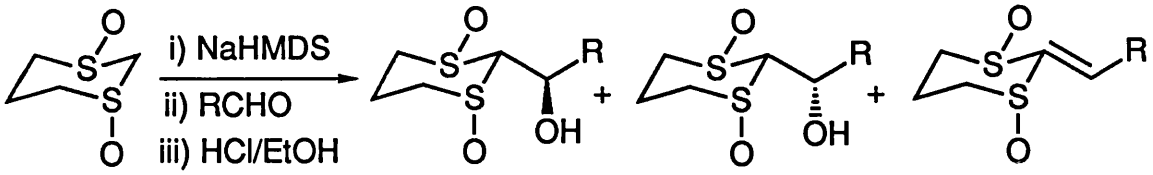


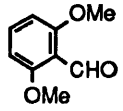
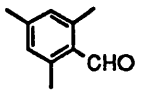
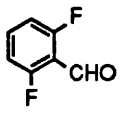
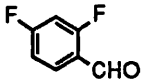
Figure 63

It is difficult to rationalise the selectivities in tables 3 and 4, with no trends emerging with respect to the properties of the aldehydes or counterions used. The exception for aromatic aldehydes with a sodium anion was the reaction with 2,6-dimethoxybenzaldehyde. Other 2,6-disubstituted aromatic aldehydes were therefore reacted in the hope that this may provide more information about this inconsistent result. The results are summarised in table 5. Again, two

reactions were performed with each aldehyde, the first monitored by HPLC to determine the best selectivity, and the second to obtain a yield.



(63) (a) (b) (c)

Entry	Product Ref^n.No.	Aldehyde	Ratio (a):(b)	Equil^n. time/mins	Isolated yields			Reaction time/mins
					(a)	(b)	(c)	
1	(97)		70:30	60	66%[a]		-	60
2	(106)		60:40	10	26% (47%)[b]		15%[c] (51%)[b]	5
3	(107)		60:40	30	25%	35%	22%	1
4	(108)		97:3	30	34%	-	41%	18

a : Combined yield of (a) and (b), which could not be separated.

b : Yield based on recovered starting material.

c : Combined yield of (b) and (c), which could not be separated.

Table 5

Mesitylaldehyde (entry 2) gave a poor selectivity, similar to that from 2,6-dimethoxybenzaldehyde. The yield of adducts was also poor for this aldehyde and over 50% of the starting material was recovered. Another problem with this aldehyde was that elimination was rapid, (hence the short "equilibration time" quoted in table 5, after this the majority of the product composition was made up of eliminated material, (**106c**)). The major

isomer (**106a**) could be isolated, albeit in low yield, from the preparative reaction. The minor isomer (**106b**) and eliminated product (**106c**) could not be separated. To obtain a pure sample for characterisation, the reaction was carried out at -78 °C with Li-(**63**). No elimination occurred under these conditions.

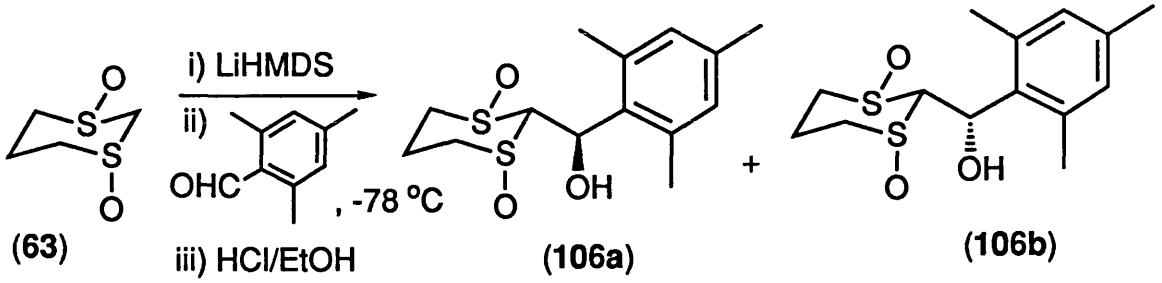


Figure 64

The two isomers (**106a**) and (**106b**) were produced in a 1:1 ratio. A pure sample of (**106b**) was obtained in 9% yield.

In the light of the results with 2,6-dimethoxybenzaldehyde and mesitylaldehyde, it was thought that the good selectivities obtained with most aromatic aldehydes could be due to the flatness of the aromatic ring. Steric interactions in one of the adducts could be reduced as a consequence of this, hence favouring its formation under the equilibrating conditions. 2,6-Disubstituted aromatic aldehydes cannot adopt a planar conformation due to the interaction of the three adjacent substituents on the aromatic ring, and the carbonyl will be pushed out of plane, figure 65.

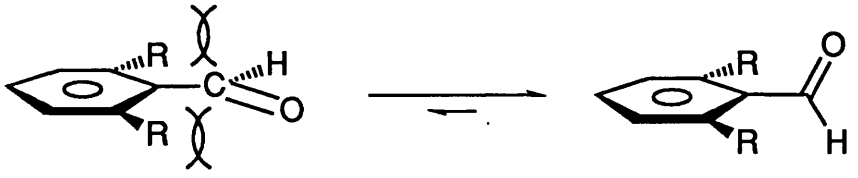


Figure 65

This could explain the poor selectivities obtained with these aldehydes. When the reaction was performed with 2,6-difluorobenzaldehyde a 60:40 ratio of adducts (**107a**) to (**107b**) was obtained; entry3, table 5. This result suggests that the above hypothesis is incorrect. The small size of fluorine should allow 2,6-difluorobenzaldehyde to adopt a planar conformation, but again poor selectivity was achieved. There was some concern about the rapid elimination that

occurred with 2,6-difluorobenzaldehyde; in the preparative reaction the eliminated product (**107c**) was isolated in 22% yield after only 1 minute reaction time. If the major isomer (**107a**) eliminated at a faster rate than the minor (**107b**) then this could reduce the observed selectivity. It was important to know if the poor ratio obtained was a true reflection of the thermodynamic ratio or just a manifestation of different rates of elimination of the adducts.

A general trend for the propensity of aromatic adducts to eliminate had now become apparent. It seems that the more electron withdrawing the aromatic ring the greater the rate of elimination. The *o*-methoxybenzaldehyde reaction could be left overnight, with very little elimination occurring. The rate of elimination then increases from benzaldehyde to *p*-nitrobenzaldehyde to 2,6-difluorobenzaldehyde. A reaction was attempted with the highly electron withdrawing pentafluorobenzaldehyde, but only the eliminated product (**109**) was observed, even after only 1 minute.

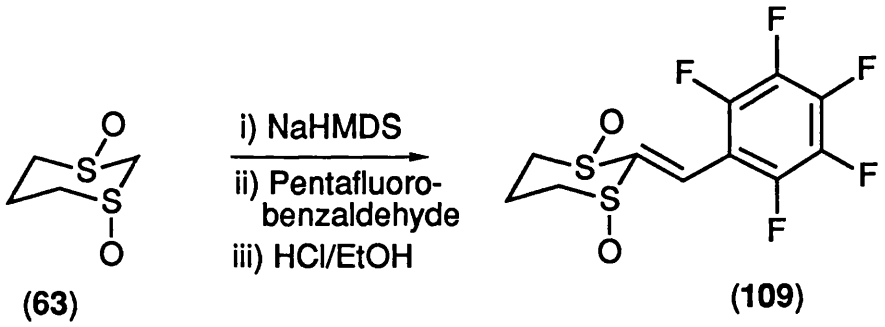


Figure 66

In order to provide some confidence in the result with 2,6-difluorobenzaldehyde, 2,4-difluorobenzaldehyde was reacted with Na-(**63**), entry 4, table 5. This aldehyde should have similar electron withdrawing properties to the 2,6-difluoro isomer. The rate of elimination with 2,4-difluorobenzaldehyde was also very rapid, however the selectivity was much better. A 97:3 ratio of adducts (**108a**) : (**108b**) was obtained after the same reaction time as the 2,6-difluoro reaction. This selectivity is comparable with the other non 2,6-disubstituted aromatic aldehydes in table 4. Hopefully this result adds credibility to the result with 2,6-difluorobenzaldehyde. The adducts of both of these difluorobenzaldehydes appear to eliminate at a comparable rate, but the selectivity is good with 2,4 substitution and poor with

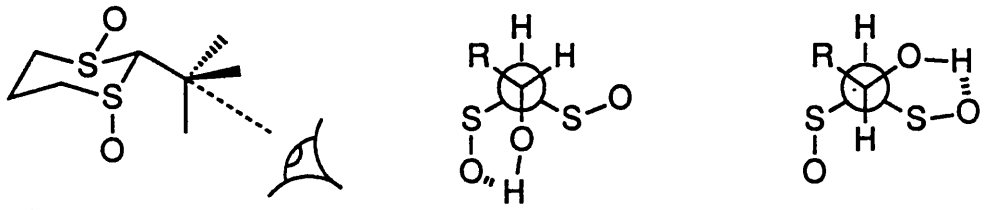
the 2,6 isomer. This seems to indicate that the ratio of adducts produced is not simply due to different rates of elimination of (**a**) *vs.* (**b**).

In order to help rationalise the selectivities some molecular mechanics calculations were performed. Twelve molecules were built for conformational analysis; these were both (**a**) and (**b**) diastereomers of the aliphatic aldehyde adducts, (**83**), (**84**) and (**85**) (table 3) and both (**a**) and (**b**) diastereomers of the aromatic aldehyde adducts (**86**), (**94**) and (**106**) (see tables 4 and 5). The molecules were systematically analysed by the SYBYL conformational search software. The global minima conformations for the (**a**) and (**b**) isomers were found to be the same regardless of the R group. They are the two H-bonded conformers shown in figure 67.

(**a**) (**b**)

Figure 67

In both of these conformations, the R group (which is the bulkiest substituent on the exocyclic carbon atom) is placed *syn* to the sulphur bearing the axial oxygen. A Newman projection reveals this to be the least sterically hindered position.



(**a**) (**b**)

Figure 68

The calculations indicated that in nearly all cases the (**b**) isomer is the more stable with the exception of R = ^{t}Bu, where (**81a**) was more stable than (**81b**). It seems that both of these ^{t}Bu isomers are highly strained molecules and this could account for the anomaly. The greater stability of (**b**) is probably predicted because the hydroxyl group in the (**b**) isomer only has

one gauche interaction, whereas in the (**a**) form it has two. This is also apparent from the Newman projection.

The calculations therefore do not agree with the experimental results, which indicate that isomer (**a**) is the major thermodynamic product. In addition the calculations did not indicate a significant difference between the aliphatic and aromatic adducts whereas experimentally their is a clear distinction. It should be noted that the calculations were performed *in vacuo* on the alcohols, whereas the experimental results relate to an equilibrium between sodium-alkoxide species in the liquid phase. However, the lowest energy conformations of the isomers were those involving a hydrogen bond and this should be a good simulation of the metal chelate of the sodium alkoxides. Also, any steric effects identified by the calculations should still be present under the experimental conditions. Therefore, the calculations are not totally invalidated.

The calculations did show that the (**a**) form of the 2,6-dimethylphenyl adduct (**106**) has a relatively high energy compared to the other aromatic adducts. This is caused by an ortho methyl group disrupting the intramolecular hydrogen bond, as shown below.

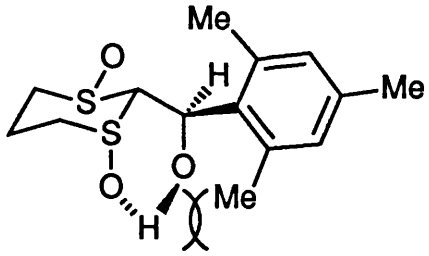


Figure 69

The same disruption does not occur in the (**b**) form. This could account for the reduced selectivity obtained with mesitylaldehyde. However, poor selectivity is also observed with 2,6-difluorobenzaldehyde and presumably the small fluorine atom will not cause the same disruption as the methyl group as in the case above.

To further investigate the importance of the counterion the reaction was carried out in the presence of a crown ether. It was feared that the crown ether may not chelate effectively in the presence of pyridine, used as the reaction solvent. Therefore *trans*-5,5-diethyl-1,3-dithiane

dioxide (**110**), prepared previously within the group[60b, 80], was used since this compound is soluble in neat THF.

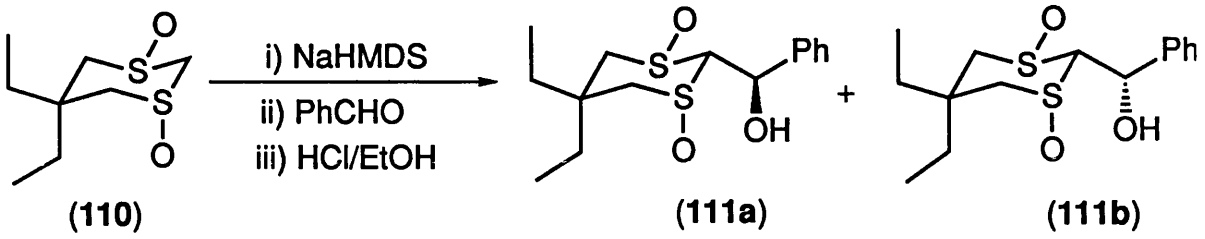


Figure 70

The dioxide (**110**) was reacted with NaHMDS and benzaldehyde at 0 °C, both with and without the presence of 18-crown-6. The selectivities obtained (approximately 90:10) were very similar in each case. The crown ether should co-ordinate strongly to the Na^+ counterion and inhibit the formation of chelates (figure 71) by the equilibrating alkoxides. Since the addition of the crown ether had no effect upon the ratio of adducts obtained then this suggests that when M = Na these chelates are not involved in determining the selectivity of the reaction. The smaller Li^+ counterion is more likely to form a chelate than Na^+ or K^+ and this may account for the differences in selectivities obtained with Li^+ compared to the latter counterions, (table 3). If sodium chelates are not being formed then this may account for the disparity between the experimental observations and the molecular mechanics calculations, which were performed on the hydrogen bonded conformers.

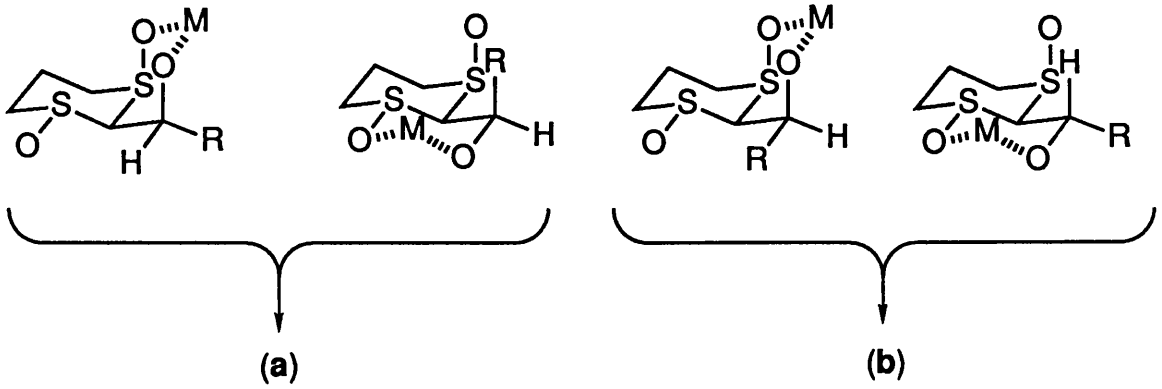
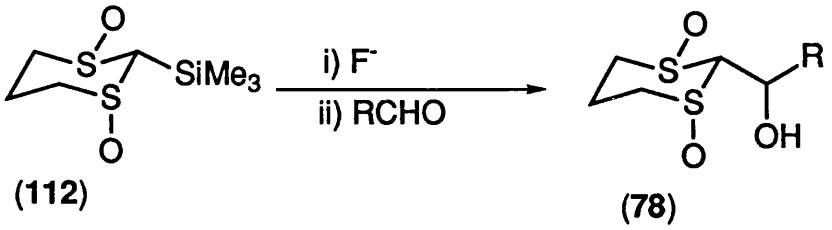


Figure 71

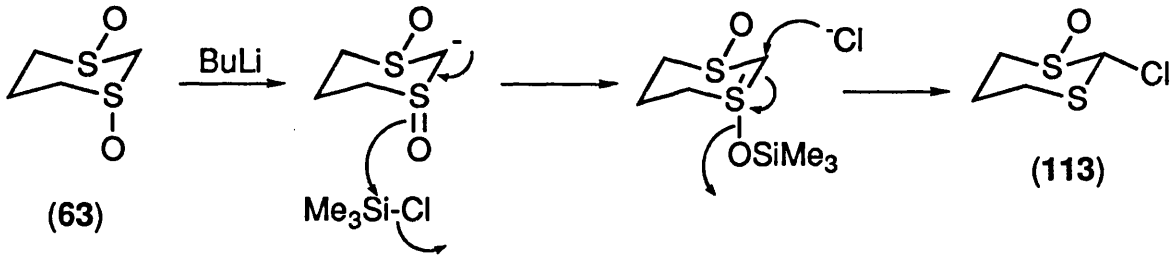
The reaction of 2-trimethylsilyl-*trans*-1,3-dithiane dioxide (**112**) with fluoride and an aldehyde, (figure 72), should allow the reaction to be carried out in the complete absence of a metal counterion.



(**112**) (**78**)

Figure 72

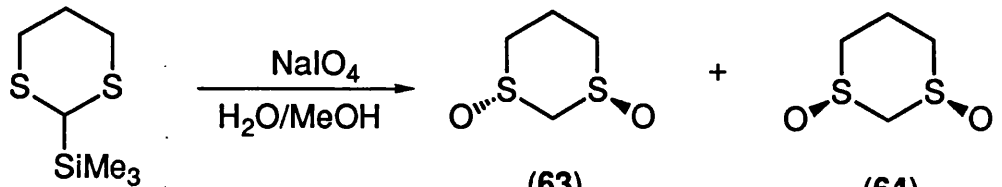
The result of such a reaction should give more information about the importance of metal chelates in determining the selectivity. The preparation of (**112**) was therefore attempted. It had been found by another member of the group[73] that the reaction of metallated (**63**) with trimethylsilyl chloride results in a silyl Pummerer reaction occurring, to give 2-chloro-1,3-dithiane-1-oxide (**113**), figure 73.



(**63**) (**113**)

Figure 73

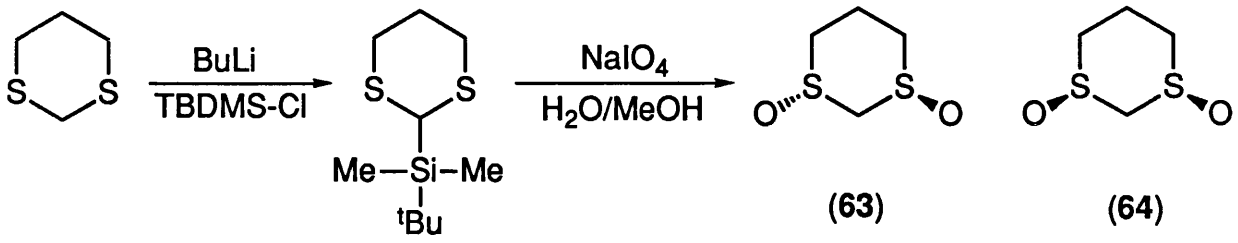
The preparation of (**112**) was therefore attempted by oxidation of 2-trimethylsilyl-1,3-dithiane (**114**) with sodium periodate. However, the trimethylsilyl group was hydrolysed under the reaction conditions and only the non-silylated dioxides (**63**) and (**64**) were obtained.



(**114**) (**63**) (**64**)

Figure 74

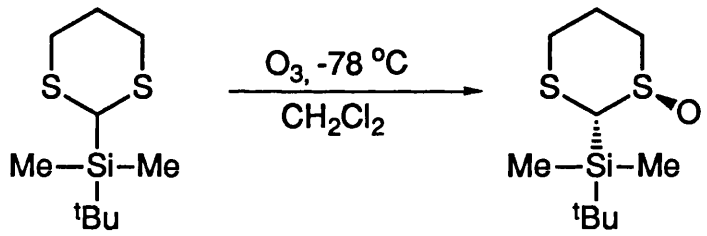
The less labile TBDMS group was therefore used in the hope that this would withstand the oxidation conditions. 2-*tert*-Butyldimethylsilyl-1,3-dithiane (**115**) was prepared by reaction of 1,3-dithiane with butyllithium and TBDMS-Cl. However, once again only the desilylated dioxides were obtained after sodium periodate oxidation, figure 75.



(115) (63) (64)

Figure 75

The oxidation of (**115**) was also performed with ozone. Since this reaction can be carried out in an aprotic solvent, this may reduce the chance of the silyl group being hydrolysed.



(115) (116)

Figure 76

Only the monoxide (**116**) could be isolated from this reaction. Longer reaction times led to decomposition products.

The lability of α-trimethylsilyl sulphoxides has been previously noted[81] and a marked stereochemical dependence has been demonstrated[81c,d]. In the oxidation of 2-trimethylsilyl-1,3-dithianes Carey[81d] has attributed the high stereoselectivity of the reaction to the decomposition of the isomer with the trimethylsilyl group *cis* to the sulphoxide, figure 77.

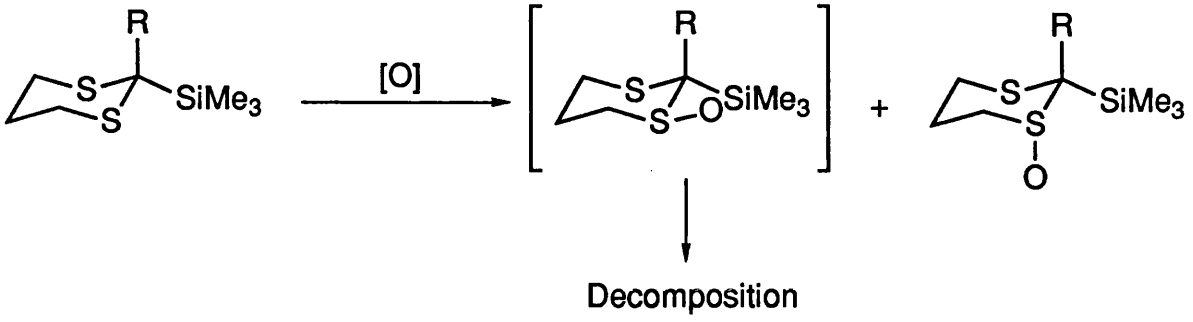


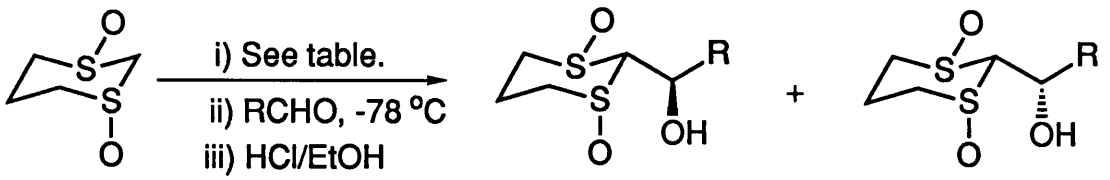
Figure 77

In a 2-silylated-1,3-dithiane *trans* dioxide the silyl group will always be *cis* to one of the sulphoxides and therefore presumably highly labile which would account for the failure to isolate such compounds.

3.2.4 Investigation of Kinetically Controlled Reactions.

The effect of solvent and the temperature of formation of the anion upon the kinetic selectivity of the reaction of (**63**) with aldehydes has already been mentioned. This short section describes the results obtained in studying the effect of different counterions upon the kinetic selectivity.

There have been several reports in the literature where the diastereoselectivity of reactions of α-sulphinyl carbanions has been improved by using counterions other than lithium[82]. Reactions of (**63**) with sodium, magnesium and zinc as counterions were investigated. The results obtained are summarised in table 6.



(63) (a) (b)

Entry	Conditions, i)	Aldehyde	Ratio (a):(b)	Comments
1	NaHMDS	PhCHO	76:24	-
2	LiHMDS, $MgBr_2$	^{n}BuCHO	50:50	-
3	MeMgBr	PhCHO	-	Only starting material present.
4	PhMgBr	PhCHO	34:66	75% Starting material left.
5	^{t}BuMgBr	PhCHO	-	Only starting material present.
6	BuLi, Et_2AlCl	PhCHO	-	No identified products.
7	BuLi, Et_2AlCl	^{t}BuCHO	-	No identified products.
8	LiHMDS, $ZnCl_2$	^{n}BuCHO	-	Only starting material present.
9	LiHMDS, $ZnCl_2$	^{i}PrCHO	68:32	-
10	LiHMDS, $ZnCl_2$	PhCHO	7:93	34% Isolated yield of (**86b**).

Table 6

Na-(**63**) gave a 3:1 ratio of adducts with benzaldehyde, (entry 1). Transmetallation of the LiHMDS derived anion of (**63**) with $MgBr_2$ followed by reaction with valeraldehyde (entry 2) led to a 1:1 mixture of adducts. Magnesium counterions to α-sulphinyl carbanions have been generated by the use of Grignard reagents as bases[83]. The Grignard reagents MeMgBr, PhMgBr and ^tBuMgBr (entries 3-5) were used as the base in the reaction of (**63**) with benzaldehyde. Only PhMgBr gave any adducts, although there was a lot of starting material present and the selectivity was poor (2:1). Attempted transmetallation with diethylaluminium chloride[84], (entries 6-7) resulted in decomposition of (**63**). Some success was achieved after transmetallation with $ZnCl_2$. The reaction of the zinc anion of (**63**) with benzaldehyde gave a 7:93 ratio of adducts, in favour of isomer (**b**), (entry 10). However, isobutraldehyde gave a 70:30 ratio in favour of isomer (**a**), (entry 9). The reactivity of Zn-(**63**) at -78 °C was rather low, as has been noted with other zinc α-sulphinyl carbanions[82a], and a large amount of starting material (*ca.* 50%) was apparent from the HPLC traces of these reactions. With valeraldehyde (entry 7), no reaction occurred and only starting material could be detected. The reaction of Zn-(**63**) with benzaldehyde was repeated on a preparative scale, to give (**86b**) in 34% isolated yield.

It is notable that of the reactions in table 6 the only good selectivity was achieved with benzaldehyde, but now in favour of isomer (**b**) rather than isomer (**a**). Isomer (**a**) is strongly favoured in the reaction of aromatic aldehydes and Na-(**63**) under equilibrating conditions.

3.3 Conclusion.

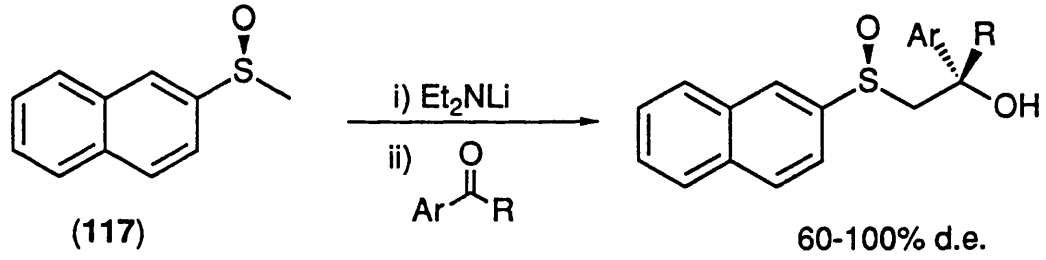
It is difficult to rationalise the results obtained in the reactions of (**63**) with aldeyhydes. The selectivity seems to be highly dependent on three main factors; the temperature at which the reaction is performed, the metal counterion present and the aldehyde used.

At 0 °C, under equilibrating conditions the combination of a sodium counterion with aromatic aldehydes led to excellent selectivity in almost all cases. The crown-ether experiments and molecular mechanics calculations suggest that a non-chelating counterion is required. The reason for aromatic aldehydes giving good selectivity is unclear, although the presence of an

ortho hydrogen seems to be important, since 2,6-difluorobenzaldehyde gave poor selectivity. There may be a favourable interaction between the *ortho* hydrogen on the aromatic ring and one of the sulphinyl groups of (**63**).

At -78 °C, under kinetic control, only a few reactions have been tried, but once again the only good result was achieved with an aromatic aldehyde, now with a zinc counterion, and with reversed selectivity to that obtained under equilibrating conditions. The Zn^{2+} counterion is small (0.69 Å)[85] with a double positive charge and therefore could form stronger chelates than the other metals tried, and this may be important in determining the selectivity at -78 °C. More results are needed before any firm conclusions can be drawn about kinetic selectivity.

It is interesting to note that there are several examples of highly selective addition reactions of aryl sulphoxides with aromatic aldehydes[25, 28, 30, 86] (see; 1.4.1 figures 20[25] and 23[28], 1.4.2 figure 30[30]). Sakuraba obtained excellent selectivity in the addition of (S)-lithiomethyl-1-naphthyl sulphoxide (**117**) to aromatic ketones[86].



(**117**) 60-100% d.e.

Figure 78

The selectivity was attributed to a π–π stacking interaction in the transition state of the favoured diastereomer, figure 79.

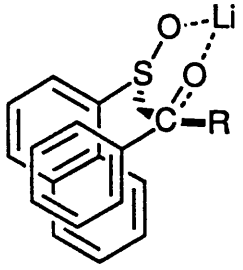


Figure 79

No such interactions are possible with *trans*-1,3-dithiane dioxide (**63**). The nature of the factors which contribute to high selectivity for aromatic aldehydes and (**63**) remains unclear.

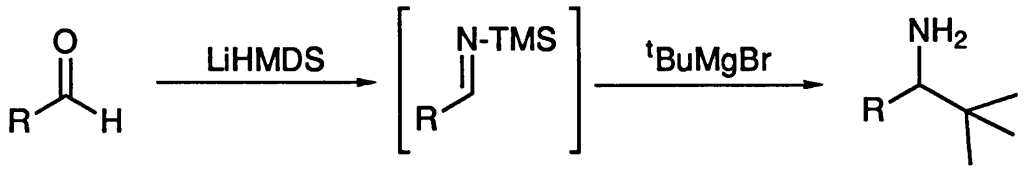
CHAPTER 4. ADDITIONS TO IMINES.

4.1 Introduction.

4.1.1 Nucleophilic Additions to Imines.

The inability of certain nucleophiles to add to the carbon-nitrogen double bond of imines, and their derivatives, coupled with the propensity of basic reagents to preferentially abstract protons α to the imine double bond has limited the utility of the group in synthetic organic chemistry[87]. For example, enolizable aldimines and ketimines are inert to addition of alkyl Grignard reagents and in their presence will undergo complete enolization in refluxing THF[88].

A number of methods have been developed to increase the reactivity of the carbon-nitrogen double bond. Hart[89] *et al.* have shown that activated *N*-trimethylsilylimines (**118**) can be generated *in situ.* and reacted with organolithium and Grignard reagents to give primary amines, figure 80.



(118)

Figure 80

Yamamoto[90] and co-workers have developed the use of α-ethoxycarbamates as a means of increasing imine reactivity. The addition of a Lewis acid and either an organo lead or an organo zinc reagent to the α-ethoxycarbamate (**120**) led to the preparation of secondary amines. The corresponding aldimines (**119**) did not undergo alkylation with these reagents, suggesting that the intermediate acyliminium ion generated from (**120**) is more electrophilic than the aldimine. This method has been applied to both enolizable and non-enolizable imines.

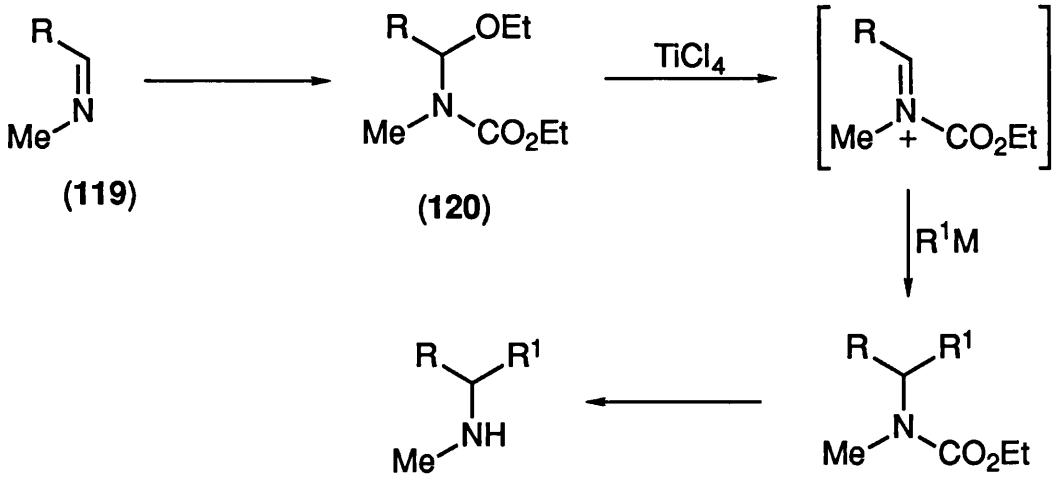


Figure 81

Lewis acid promoted addition methodology has also provided a solution to the problem of imine reactivity. In the presence of MgX_2, organo-cadmium and -zinc compounds add smoothly to imines derived from aromatic aldehydes and aryl amines. Yields are very low if the reactions are performed in the absence of a Lewis acid promoter[91]. A catalytic amount of Lewis acid, such as ZnI_2, $AlCl_3$, $TiCl_4$, $Al(OPr^i)_3$, *etc.*, promotes the addition reactions of TMS-CN to imines, giving *N*-TMS-α-aminonitriles[92]. The product is a useful precursor to α-aminonitriles, α-aminoamides or α-aminoacids. Asymmetric induction has been incorporated into this methodology. α-Aminonitriles (**122**) could be produced in 57-69% d.e. by cyanosilylation of (-)-*N*-alkylidene-(1-methylbenzyl) amines (**121**) catalyzed by $ZnCl_2$.

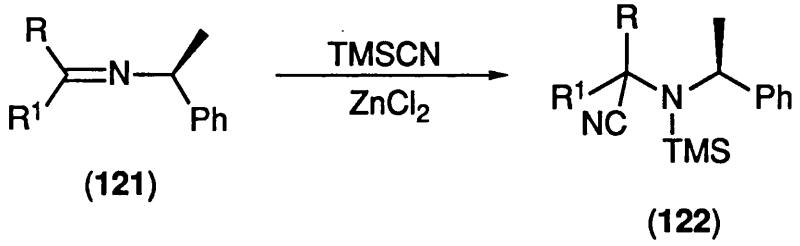


Figure 82.

Optical purities of the adducts obtained by the Lewis acid promoted reaction are much higher than those attained by the simple addition of hydrogen cyanide to imines.

Weinreb[93] has accomplished the addition of Grignard and organolithium reagents to imines by activation with *N*-sulphonyl groups.

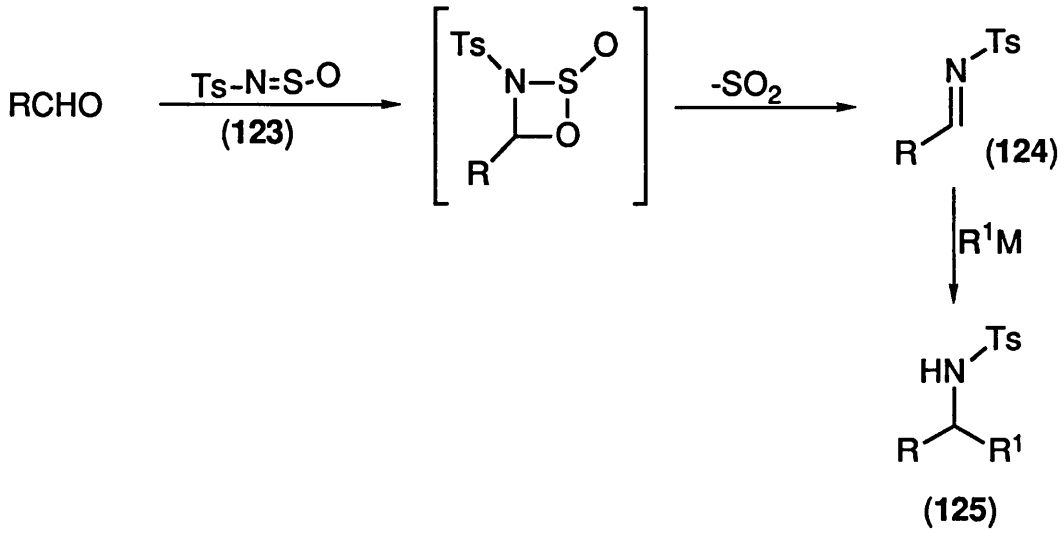


Figure 83.

Addition of *N*-sulphinyl-*p*-toluene sulphonamide (**123**) to an aldehyde led to conversion to an *N*-tosyl imine (**124**), (a Lewis acid was required in the case of aromatic aldehydes). Without isolation, the *N*-tosyl imine could be reacted with an organometallic reagent to afford the *N*-tosyl amines (**125**). This methodology has been demonstrated with a wide range of examples. A few examples using the (β-(trimethylsilyl)ethyl)sulphonyl, (SES) group were also reported. A typical reaction is shown in figure 84.

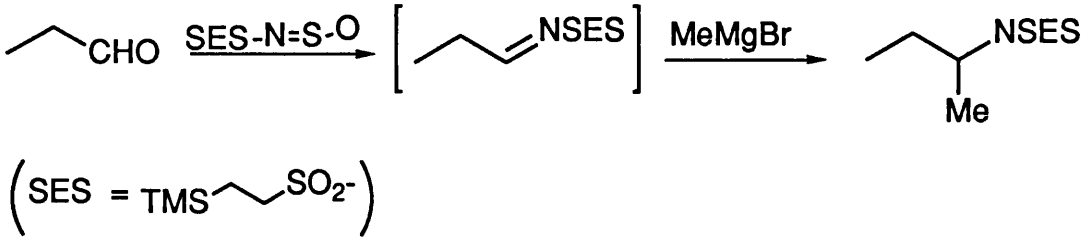
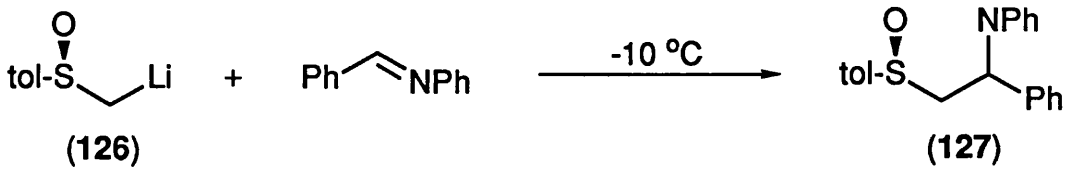


Figure 84.

The ease of removal of the SES group[94a] may make it superior to the tosyl activating group.

4.1.2 Addition of α-Sulphinyl Carbanions to Imines.

There are few examples in the literature of α-sulphinyl carbanion additions to imines. Tsuchihashi[94b] first reported the addition of the lithiated sulphoxide (**126**) to *N*-benzylideneaniline, figure 85.

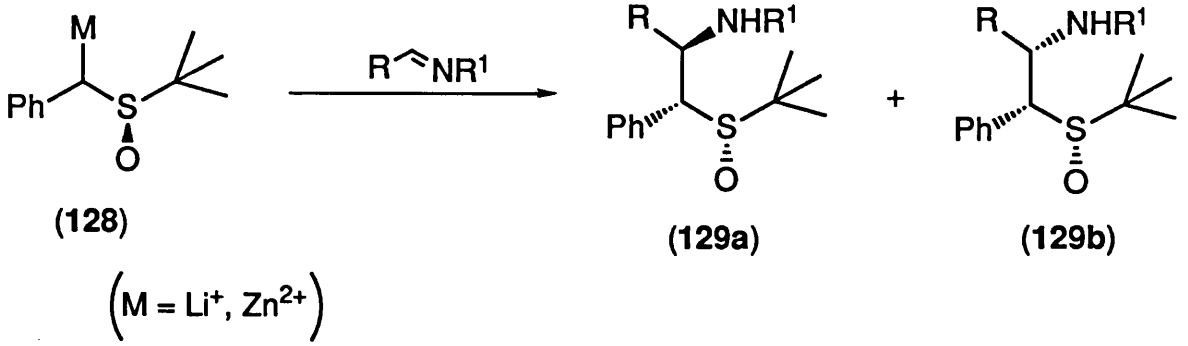


(126) (127)

Figure 85

It was stated that the product, (**127**) was isolated as a single diastereomer. A more thorough investigation of the reactions of (**126**) by Kagan[74] gave (**127**) as a 3:1 mixture under the same conditions. Kagan reported reactions with a wide range of *N*-aryl and *N*-alkyl aromatic imines. Under optimal conditions (deprotonation at 0 °C and reaction at -78 °C) a d.e. of 88% was obtained for the reaction in figure 85.

Pyne and co-workers have made several reports of their studies in this area[82c, 95-98].



(128) (129a) (129b)

$(M = Li^+, Zn^{2+})$

Figure 86

The reactions of lithium-(**128**) or zinc-(**128**) with *N*-phenyl aromatic imines proceeded in good yield and gave excellent diastereoselectivities (>97:<3)[82c]. Reactions with *N*-alkyl aromatic imines were problematic. The reaction with *N*-benzylidenemethylamine (R = Ph, R^1 = Me), only occurred with zinc-(**128**) and precomplexation of the imine with a Lewis acid was required to obtain a reasonable yield. The selectivity of the reaction, however, was modest with a 58:42 ratio of (**129a**) and (**129b**) produced. Reaction with enolizable imines (R = alkyl) did not give any adducts and it was thought this was due to α-proton abstraction from the imine and subsequent polymerisation.

Pyne has also reported reactions of lithiated methyl *p*-tolyl sulphoxide (**126**) with imines[95]. It was found that at 0 °C the reactions were under thermodynamic control, with equilibration of

the adducts occurring. At -78 °C the reaction proceeded under kinetic control. In general product selectivities were better at -78 °C. An exception to this was the reaction with 3,4-dihydro-6,7-dimethoxyisoquinoline (**130**) where the best selectivity (8:92) was observed under equilibrating conditions.

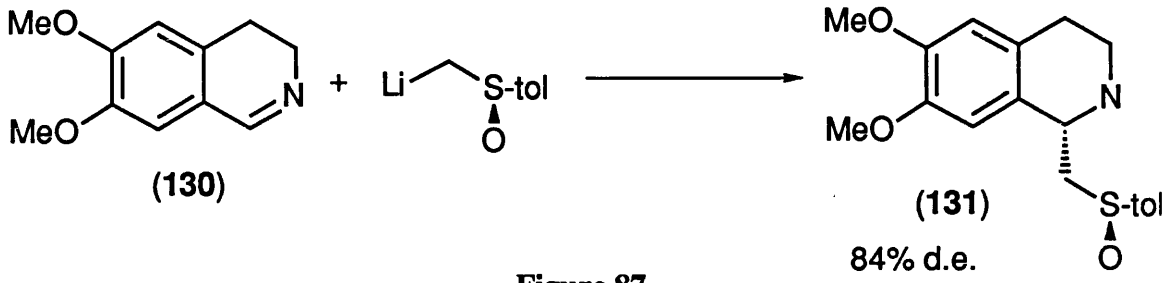


Figure 87

Again it was noted that *N*-alkyl imines are not suitable substrates. Clearly, aryl substituents on the imine that can stabilise incipient charge in the transition state are important to ensure high chemical reactivity in these reactions. This methodology has been applied to the total synthesis of (R)-(+)-tetrahydropalmatine (**132**)[96].

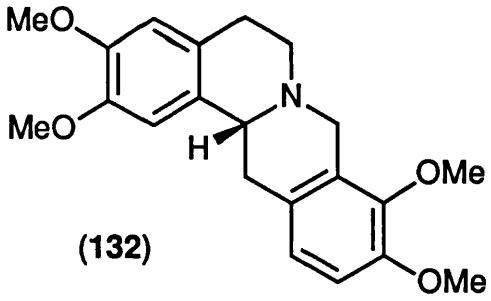
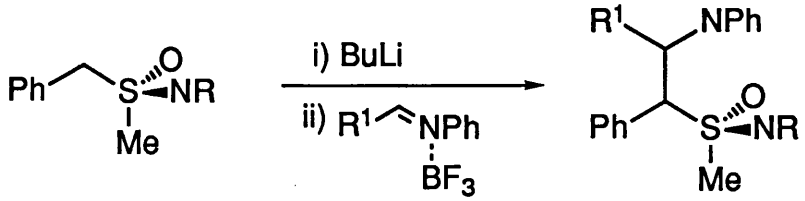


Figure 88

From the results with (**126**) and (**128**), Pyne concluded that a bulkier substituent on sulphur increased the selectivity of the reaction. This line of thinking was extended by investigation of the sulphoximes (**133**) and (**134**)[97, 98].

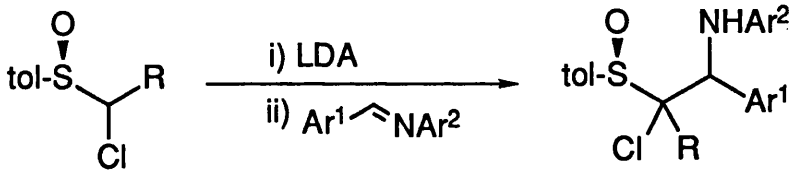


(**133**) R = $SiPh_2{}^tBu$
(**134**) R = $SiMe_2{}^tBu$

Figure 89

Good selectivities were achieved (typically 95:5) in the reaction of the *N*-^{t}butyldiphenylsilyl-sulphoximine (**133**) with butyllithium and a variety of both aromatic and enolizable *N*-phenyl imines. Reduced yields and selectivities were obtained if the non-complexed imine was used. The analogous reactions of *N*-^{t}butyldimethylsilylsulphoximine (**134**) were less diastereoselective. It appears that highly sterically demanding substituents are required at the sulphoximine nitrogen to ensure high diastereoselectivity in these reactions.

Yamakawa and co-workers[99,100] have studied the addition of 1-chloroalkyl *p*-tolyl sulphoxides (**135**) to *N*-aryl aromatic imines.



(135) **(136)**

Figure 90

Excellent diastereoselectivity was observed, with the chloroamines (**136**) isolated as single diastereomers. The asymmetric synthesis of chiral aziridines (**137**) and secondary amines (**138**) has been achieved using this methodology.

(137) **(138)**

Figure 91

4.1.3 The Asymmetric Synthesis of α-Amino Acids from *trans*-1,3-Dithiane Dioxide?

It was proposed to investigate the addition of *trans*-1,3-dithiane dioxide (**63**) to imines. The current hydrolysis procedure for the dithiane dioxide moiety, developed for the aldehyde adducts of (**63**), transforms the C-2 carbon of the dithioacetal into a carboxylic acid derivative (see chapter 5). If the adducts of (**63**) with imines can be hydrolysed in an analogous way

then selective additions to imines could lead to the asymmetric synthesis of α-amino acid derivatives (**139**), figure 92.

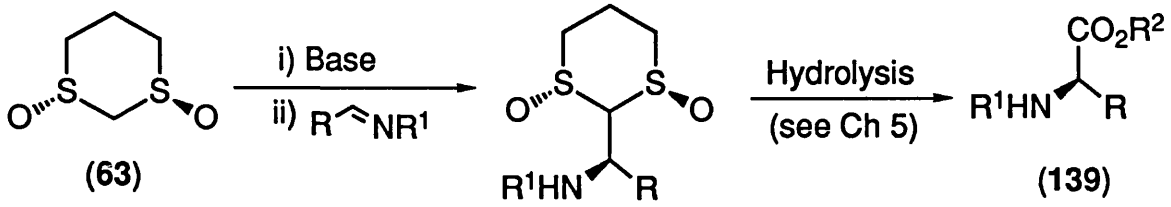


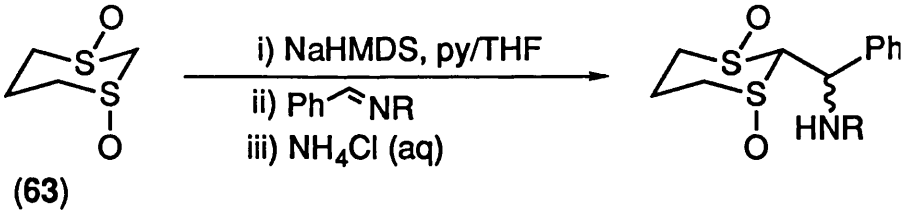
Figure 92

The results obtained towards this goal are described in the following section.

4.2 Results and Discussion.

In view of the problems involved in the reactions of enolizable imines, and since good selectivities were obtained with (**63**) and aromatic aldehydes, it was decided to investigate the addition to aromatic imines.

The *N*-phenyl and *N*-benzyl imines, benzylideneaniline and benzylidenebenzylamine were reacted with Na-(**63**), at -78 °C. The results are shown in table 7.

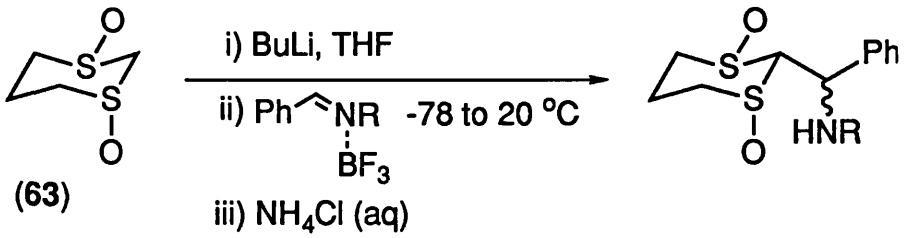


Entry	Prod. Refn. No.	R	Ratio (a):(b)	Yield ((a)+(b))
1	(140)	CH_2Ph	-	-
2	(141)	Ph	84:16	10%

Table 7

The *N*-benzyl imine gave no products at all and only starting material was isolated, entry 1. The adducts (**141**) were obtained in low yield with the *N*-phenyl imine. A moderate selectivity was achieved but the isomers were not separable by column chromatography.

The reactions were then repeated but with the imines precomplexed with BF_3 etherate, see table 8.



(63)

Entry	Ref[n.]	R	Ratio (a):(b)	Yield ((a)+(b))
1	(140)	CH_2Ph	57:43	31%
2	(141)	Ph	81:19	17%

Table 8

There was some concern that using a Lewis acid with pyridine as the solvent would result in the Lewis acid complexing to the pyridine rather than the imine. Therefore reactions were carried out in neat THF. Since starting the project, studies within the group have shown that reaction of (**63**) in neat THF is possible by dissolving a finely ground powder in a large amount of THF[101]. The *N*-benzyl imine did give products, (**140**), under these conditions, (entry 1) although in poor yield and with little selectivity. A slightly increased yield was observed with the *N*-phenyl imine compared to that obtained in the absence of a Lewis acid promoter, the selectivity however was not improved.

The Lewis acid promoted reaction with benzylideneaniline (entry 1) has also been repeated in pyridine/THF, and an almost identical result was obtained, in terms of yield and selectivity. The imine was precomplexed to BF_3 etherate in THF before addition to Li-(**63**) in pyridine/THF. Using pyridine in the presence of Lewis acids is therefore not a problem for these reactions.

Due to the poor yields obtained with the Lewis acid promoted reactions, attention was focused on some of the other methodologies that have been used to increase imine reactivity. Using

Hart's[89] procedure the *N*-trimethylsilyl imine (**142**) was prepared *in situ* from benzaldehyde and LiHMDS, and treated with Na-(**63**). No reaction occurred, however, and only starting materials were isolated.

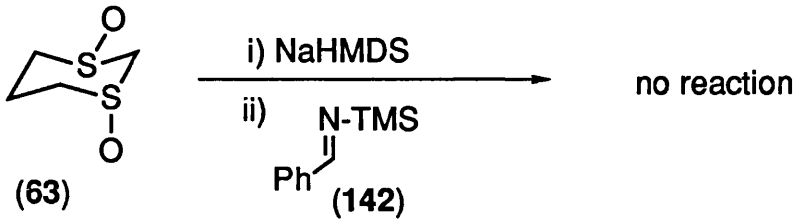


Figure 93

N-Sulphonyl imines were then investigated. *N*-Benzylidene-*p*-sulphonamide (**143**) was prepared according to Procter's procedure[102], figure 94[d] .

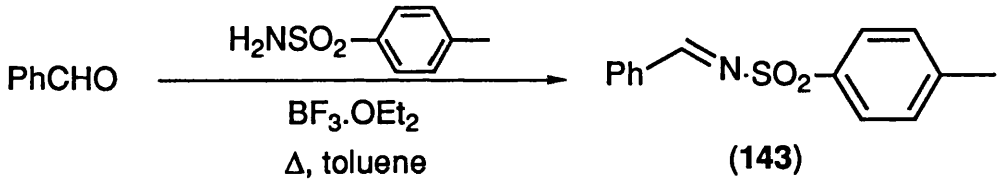
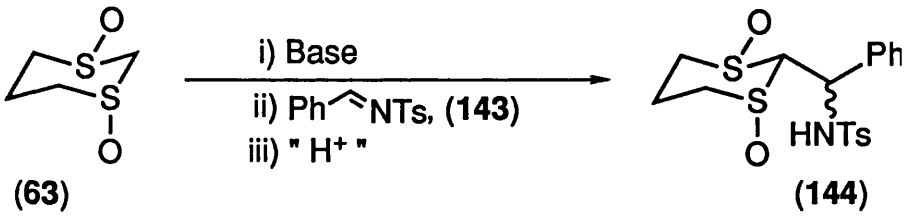


Figure 94

The anion of *trans* dithiane dioxide was reacted with the imine (**143**) under a variety of conditions, as shown in table 9.

[d].This method is only suitable for the preparation of *N*-sulphonyl imines which do not contain an α-hydrogen atom. Weinreb's procedure[93], however, which involves an *in situ* preparation (see 4.1.1) also allows the formation enolizable *N*-sulphonyl imines.



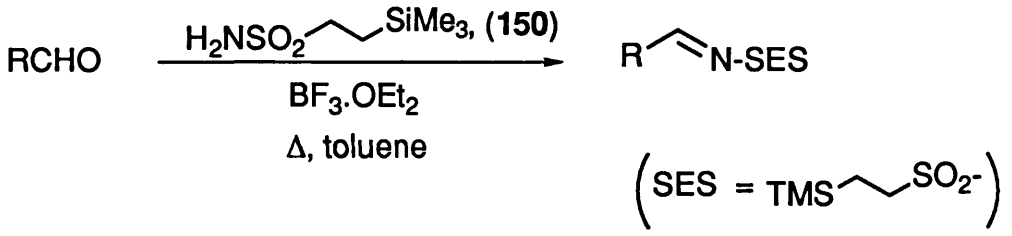
(63) (144)

Entry	Base	Temperature	Quench	Ratio (a):(b)	Yield ((a)+(b))
1	NaHMDS	0 °C	HCl/EtOH	21:79	38%
2	NaHMDS	0 °C	H_2O	18:82	19%
3	NaHMDS	0 °C	NH_4Cl	15:85	66%
4	BuLi	-78 °C	NH_4Cl	25:75	42%

Table 9

The reactions at 0 °C were monitored over a period of time, but there was no change in the selectivity from 1 minute to 16 hours. Preparative reactions were then performed to obtain yields and samples for characterisation. Three different quenches were tried, (entries 1-3). Of these, addition of saturated NH_4Cl solution provided the product (**144**) in the greatest yield. Unfortunately, as in the case of the *N*-phenyl and *N*-benzyl imine adducts, (**140**) and (**141**), the two diastereomers (**144a**) and (**144b**) were not separable and the products were characterised as a mixture. The conditions that gave good selectivity with aromatic aldehydes (0 °C, NaHMDS) gave a reasonable selectivity (85:15, entry 3), with the imine (**143**). Reaction at -78 °C with Li-(**63**) gave a very similar ratio, although the yield of the reaction was lower.

Reactions were also carried out with *N*-SES imines. The non-enolizable imines (**145**)-(**147**) were prepared in an analogous way to the *N*-tosyl imines (**143**), by refluxing the aldehyde in toluene in the presence BF_3 etherate and the *N*-sulphonyl amine (**150**), (see table 10).



Entry	Product Ref^n. No^o.	R	Yield
1	(145)	Ph	65%
2	(146)	^{t}Bu	20%
3	(147)	MeO-	70%
4	-	O_2N-	-

Table 10

The formation of this amine, as outlined in figure 95, was achieved by reaction of SES-Cl, (**149**) (prepared according to Weinreb's procedure[94]) with methanolic ammonia.

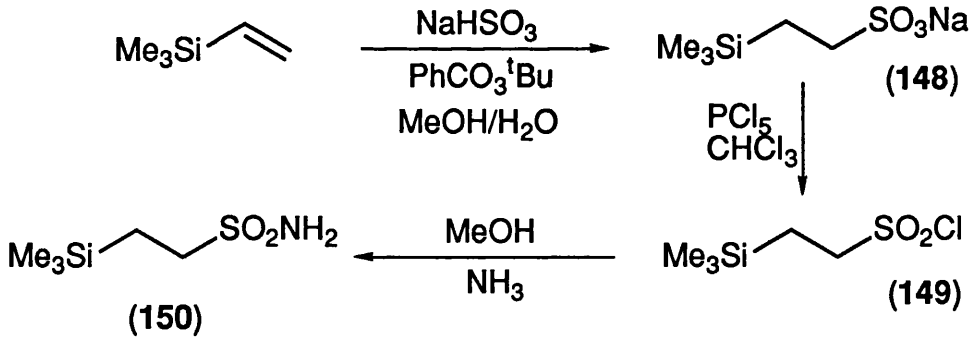
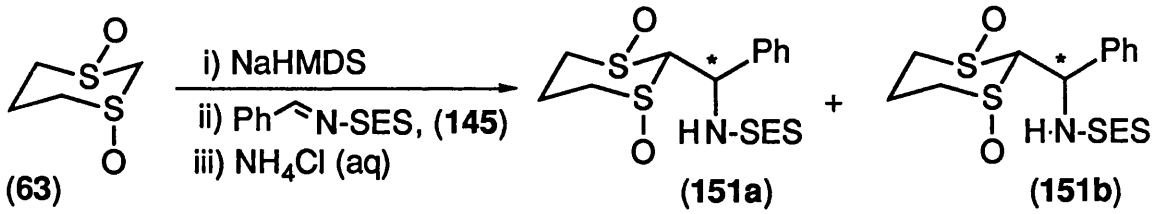


Figure 95

The phenyl *N*-SES imine (**145**) was reacted with (**63**) at 0 °C, using NaHMDS to generate the anion, to give a 60:40 ratio of adducts (**151a**) and(**151b**).



(* ; stereochemistry unknown)

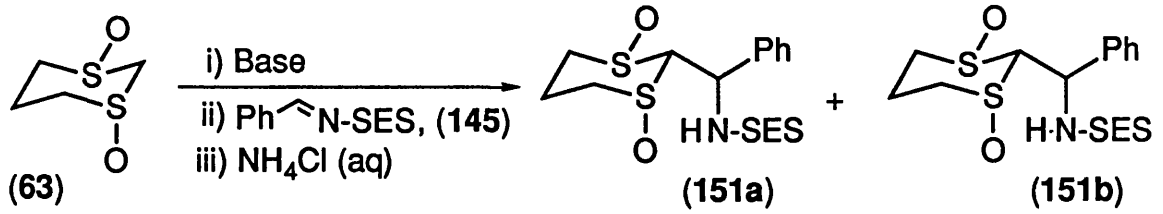
Ratio	60	:	40
Yield	16%		11%

Figure 96

As with reactions with aldehydes and the *N*-tosyl imine, the reaction was monitored over a period of time to see if the adducts were equilibrating. However, as was the case with the *N*-tosyl imine reactions the product distribution was always the same from 1 minute to 16 hours. This could either mean that the reactions are under kinetic control, or under thermodynamic control, with equilibration occurring very rapidly, within the first minute.

Unlike the analogous *N*-tosyl compounds the *N*-SES adducts could be separated by column chromatography. A preparative reaction gave relatively poor yields of pure samples of the two isomers, (**151a**) and (**151b**). No X-ray structure has been obtained for any of the imine adducts. For all but the *N*-SES compounds, this was not possible since the two diastereomers were not separable. No suitable crystals have been obtained of any of the *N*-SES adducts. There is also no clear correlation in terms of the tlc behaviour and NMR spectra between the imine and aldehyde adducts. Therefore assignment of the stereochemistry of the imine adducts has not been made.

Since pure samples of each isomer of the *N*-SES imine adducts could be obtained, it was possible to determine whether the reactions were under kinetic or thermodynamic control. Pure samples of the minor adduct (**151b**) were subjected to the reaction conditions with both LiHMDS and NaHMDS as base, at 0 °C. In both cases none of the other diastereomer could be detected, even after an hour. It was therefore concluded that reactions with *N*-sulphonyl imines are under kinetic control. To try and increase the selectivity, reactions were carried out at lower temperatures. A variety of conditions were tried, as summarised in table 11.



(63) (151a) (151b)

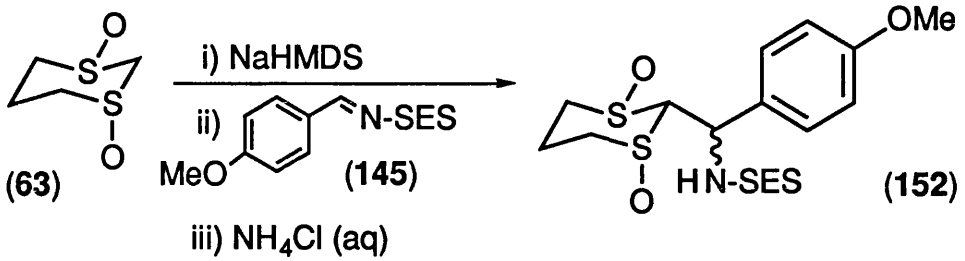
Entry	Base	Temperature	Ratio (151a): (151b)
1	NaHMDS	-78 °C	-
2	KHMDS	-78 °C	-
3	LiHMDS	-78 to 20 °C	60:40
4	NaHMDS	-78 to 20 °C	66:34

Table 11

At -78 °C, with both Na and K HMDS bases no reaction occurred, entries 1 and 2. Reactions were therefore started at -78 °C and allowed to very slowly warm to room temperature. This should mean that reaction occurs at the minimum possible temperature and, since the reactions are under kinetic control this should give rise to the greatest selectivity. The reaction with LiHMDS gave a 60:40 ratio of adducts and with NaHMDS a 66:34 ratio was obtained. This latter result is slightly better than that for the same reaction carried out at 0 °C, which gave a 60:40 ratio (figure 96).

In order to investigate other variables which may influence the selectivity of the reaction, it was decided to investigate a range of other *N*-SES imines. In the first instance it was decided to limit these to non-enolizable imines. The preparation of the electron rich and electron deficient aromatic imines, derived from *p*-methoxybenzaldehyde and *p*-nitrobenzaldehyde, was attempted along with the non-enolizable aliphatic imine derived from pivalaldehyde. Using the conditions as shown in table 10, the *N*-SES imines (**146**), R = ^{t}Bu, and (**147**), R = *p*-$MeOC_6H_4$, were obtained. The reaction with *p*-nitrobenzaldehyde, however, was not successful and the imine could not be prepared by this method.

The two imines (**146**) and (**147**) were reacted with Na-(**63**). Unfortunately no adducts could be isolated from the ^{t}butyl imine, (**146**). The *p*-methoxyphenyl imine (**147**) gave a mixture of adducts (**152**) in close to 1:1 ratio in moderate yield, figure 97.



Ratio (**152a**) : (**152b**) 53:47
Yield (**152a**) + (**152b**) 41%

Figure 97

The two diastereomers could not be separated and the adducts were characterised as a mixture.

4.3 Summary and Conclusion.

In summary, anions of (**63**) react with *N*-phenyl aromatic imines, with moderate selectivity but in very low yield. *N*-Alkyl aromatic imines will react, but only in the presence of a Lewis acid promoter, and again in poor yield and with poor selectivity. *N*-Sulphonyl aromatic imines react with Li- and Na-(**63**), under kinetic control, in low to moderate yield and with variable selectivity (6-70% d.e.). There are insufficient results to draw any firm conclusions about the factors which may influence the selectivity in the additions to *N*-sulphonyl imines, although the initial experiments suggest that the metal has little effect.

So far the *N*-SES imines look the most promising because their adducts are the only ones that have been separated, in addition the SES group should be more easily removed than the other *N*-protecting groups that have been used. It is unfortunate that selectivity results were only obtained with the two *N*-SES imines (**145**) and (**147**). With just two results it is impossible to draw any conclusions about the effect of the nature of the imine upon product distribution.

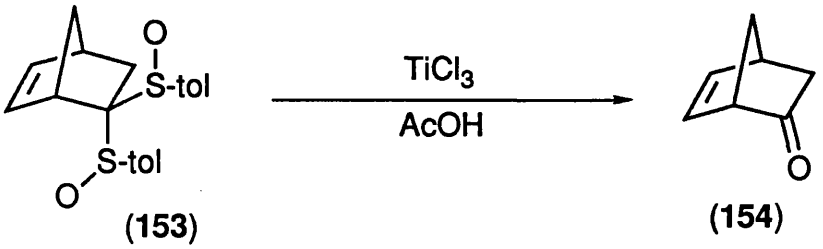
Selectivities need to be improved and a method of hydrolysis developed if the addition of (**63**) to imines is to lead to a viable asymmetric synthesis of α-amino acids, or their derivatives.

CHAPTER 5. HYDROLYSIS.

5.1 Introduction.

There are a few examples in the literature of the hydrolysis of bissulphoxides.

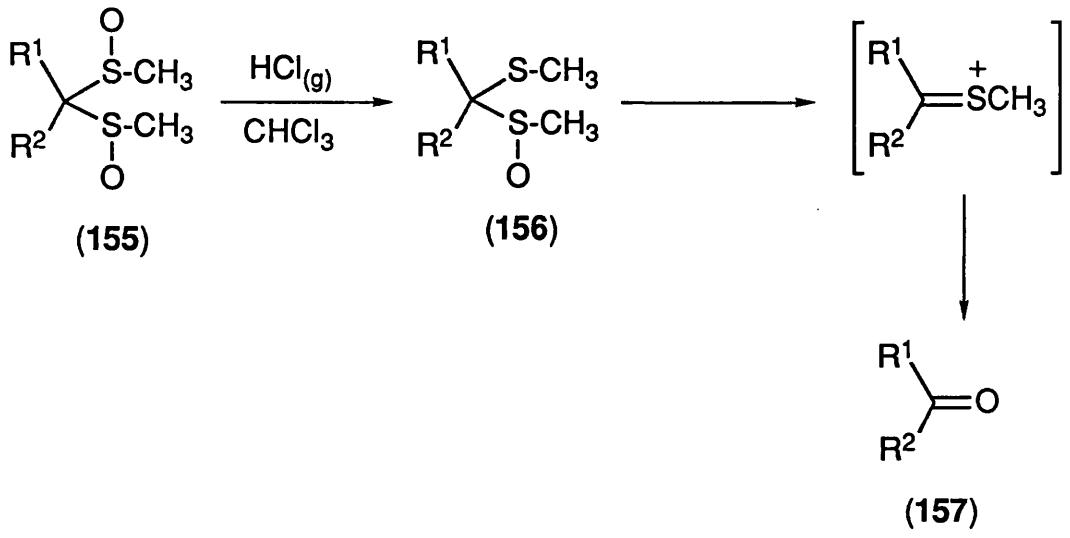
Koizumi *et al.*[103] have transformed the bis *p*-tolylsulphinyl group of (**153**) to the ketone (**154**), in 36% yield, by reaction with titanium trichloride in acetic acid.



(**153**) (**154**)

Figure 98

Louw and co-workers[104] have hydrolysed several bissulphoxides of the type (**155**), by treatment with HCl gas.



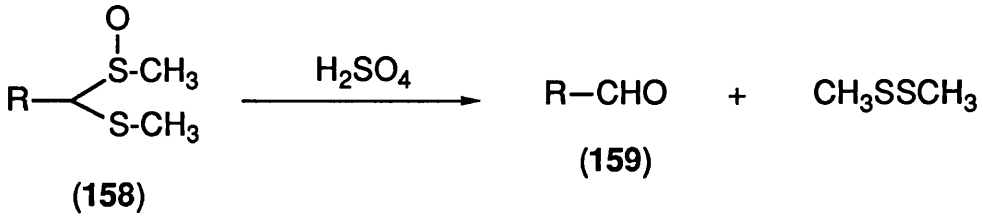
(**155**) (**156**) (**157**)

Figure 99

The mechanism of the hydrolysis involves initial reduction of the bissulphoxide (**155**) to the monosulphoxide (**156**) with concomitant oxidation of chloride to chlorine. Hydrolysis of then (**156**) gives rise to the carbonyl compounds (**157**).

There are several reports on the hydrolysis of dithioacetal monoxides.

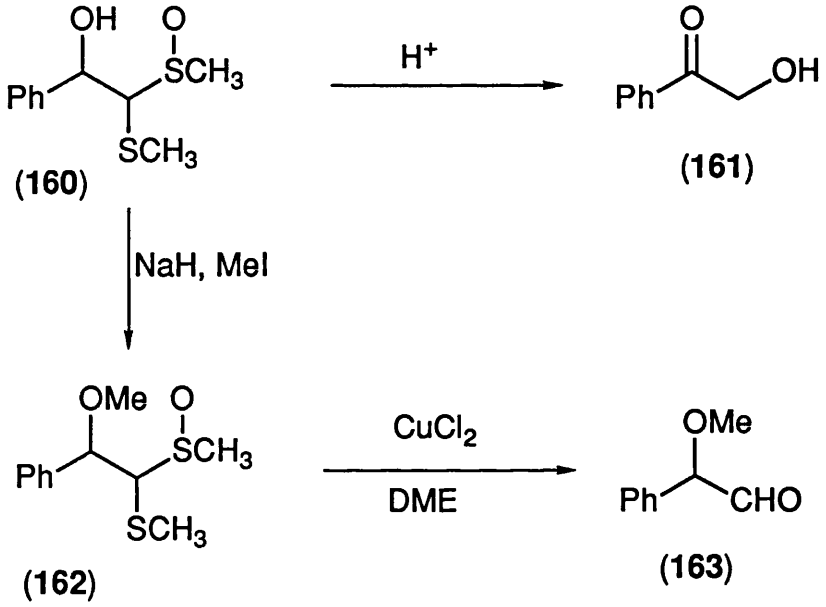
Tsuchihashi has published several examples[18, 105]. The acidic hydrolysis of compounds of type (**158**), figure 100, gave rise to the aldehydes (**159**)[18a].



(**158**) (**159**)

Figure 100

When these conditions were applied to substrates of the type (**160**)[18b], the isomerized product (**161**) was obtained.

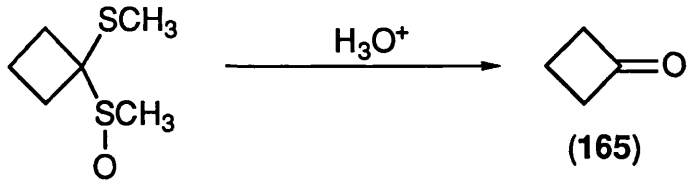


(**160**) (**161**) (**162**) (**163**)

Figure 101

Protection of the alcohol as the methyl ether (**162**), and subsequent treatment with copper (II) chloride gave the protected α-hydroxyaldehyde (**163**).

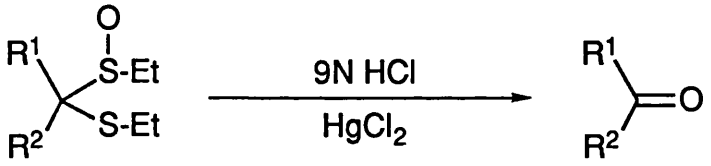
Tsuchihashi[105] has also reported the acid hydrolysis of the cyclic dithioacetal monoxide (**164**), to give the ketone (**165**).



(164) (165)

Figure 102

Herrmann *et al.*[106] have described the acid hydrolysis of the thioacetal monosulphoxides (**166**), in the presence of mercuric chloride to give the aldehyde or ketone (**167**).

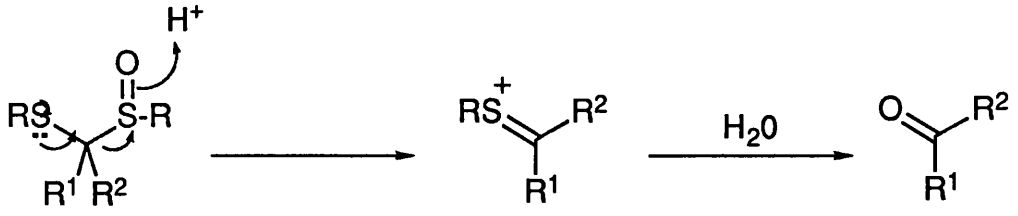


(166) (167)

Figure 103

In all the cases above, the transformation of the dithioacetal to a carbonyl involves the hydrolysis of a dithioacetal monoxide. In the first two examples the dithioacetal dioxides are reduced to the monoxide prior to the hydrolysis step.

These hydrolyses are dependent upon the availability of the sulphide lone pair during the formation of the intermediate sulphonium ion (**168**) and, under acidic conditions, the sulphoxide group is a good leaving group.



(168)

Figure 104

The direct hydrolysis of a dithioacetal dioxide will be much harder since the lone pair of the sulphoxide is much less nucleophilic due to the polarity of the sulphur-oxygen bond.

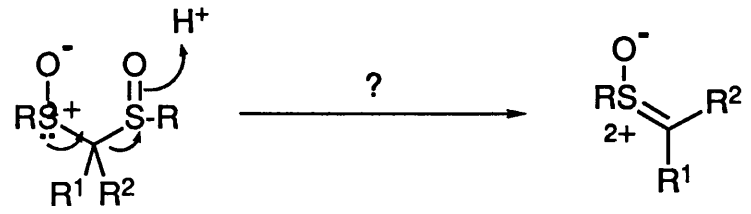
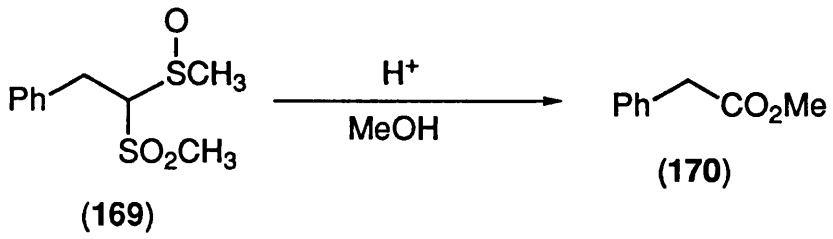


Figure 105

Therefore, if the dithiane dioxide moiety is to be hydrolysed by the normal mechanism, initial reduction will be required. To date the only reported examples of reduction and hydrolysis of bissulphoxides are either low yielding ($TiCl_3$)[103] or require severe conditions ($HCl_{(g)}$)[104].

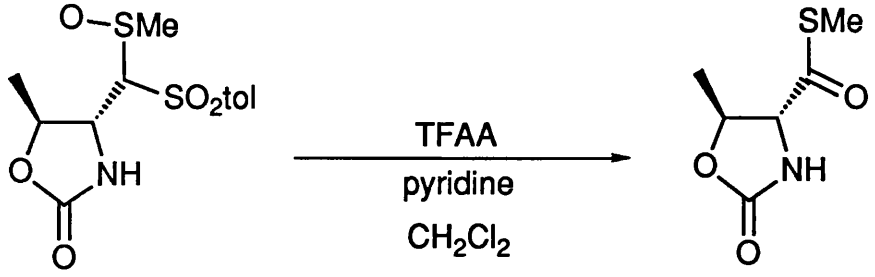
There are several literature examples of the hydrolysis of dithioacetal tris oxides. Ogura and co-workers[107] utilised a Pummerer type rearrangement and methanolysis to form the methyl ester (**170**) from the S,S,S'-trioxide (**169**).



(169) **(170)**

Figure 106

A Pummerer rearrangement, with trifluoroacetic anhydride, was used by Hirama *et al.*[108] in the transformation of (**171**) to the thiolester (**172**).



(171) **(172)**

Figure 107

These transformations involve generation of a sulphonium ion (**173**), which is then hydrolysed, with the sulphone as the leaving group, to give either the thiolester (**174**) or methyl ester (**175**).

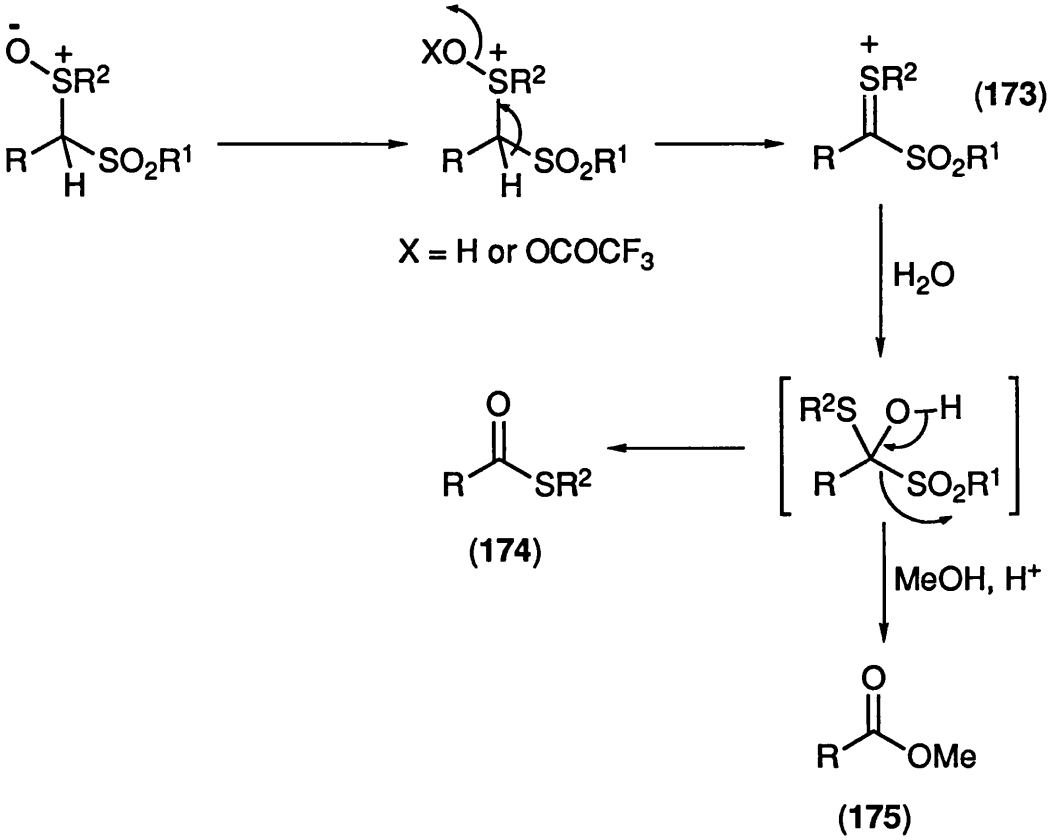


Figure 108

It was envisaged that a similar Pummerer rearrangement could be used to hydrolyse the 1,3-dithiane-1,3-dioxide moiety.

There was some concern about the possibility of epimerization at the hydroxy centre of the dithiane dioxide aldehyde adducts upon generation of the sulphonium ion (**176**).

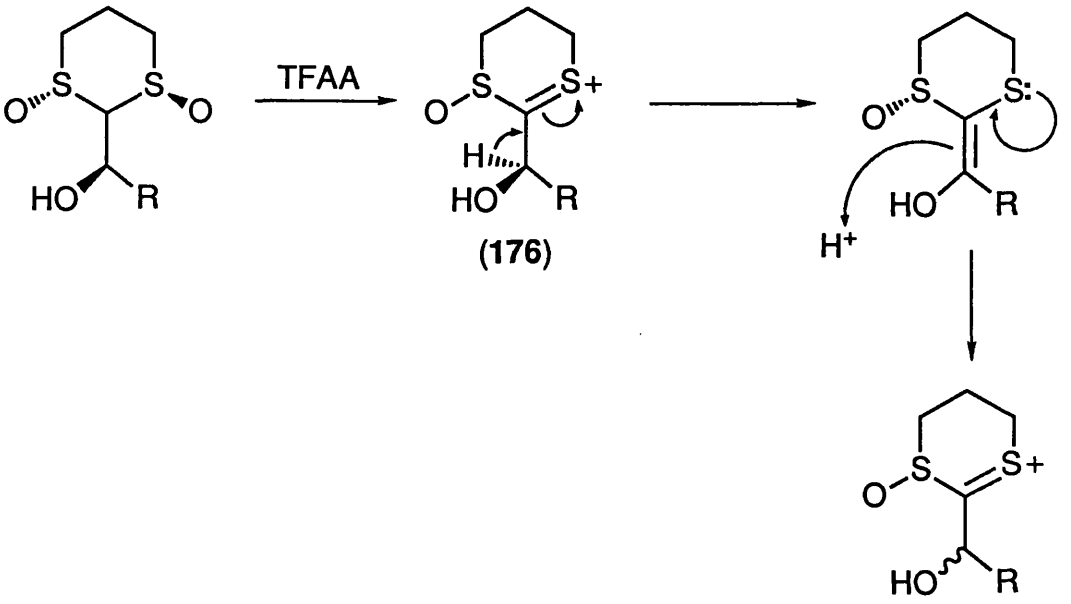


Figure 109

However, consultation with the literature has shown that there are several examples reported where sulphonium ions have been generated alpha to chiral centres with no subsequent epimerization. One such example is the reaction in figure 107 and Hirama reported isolation of the thiolester (**172**) without loss of optical purity. Kosugi and Uda[109] have carried out the transformation shown in figure 110 and confirmed the optical purity of the product (**177**).

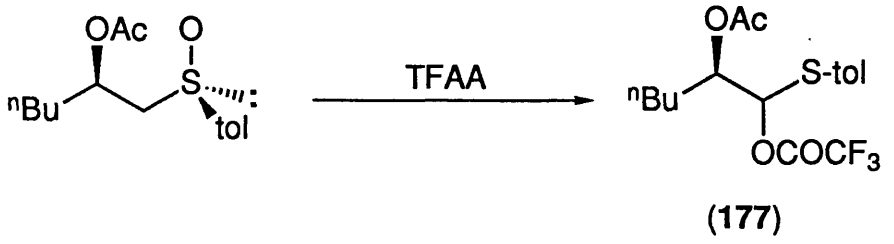
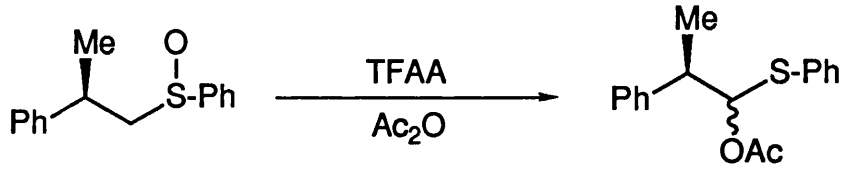


Figure 110

In the case of the aromatic aldehyde adducts of dithiane dioxide, the hydroxy chiral centre is also benzylic and therefore potentially more prone to epimerization than the chiral centres in the two examples cited above. However, Heathcock[110] has reported a Pummerer reaction of the substrate (**178**) to give a diastereomeric mixture of products (**179**) but with no epimerization at the benzylic chiral centre.



(178) (179)

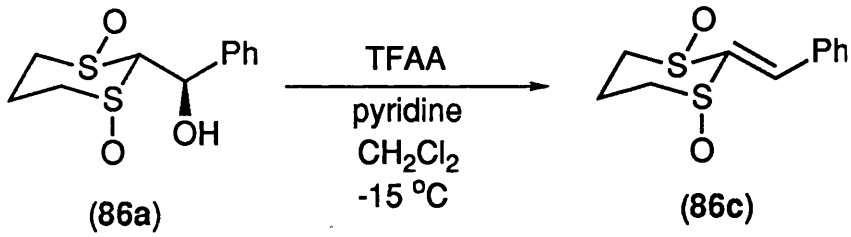
Figure 111

It was therefore thought to be viable to use a Pummerer reaction for the hydrolysis of the dithiane dioxide adducts. The development of this methodology is described in the following section of this chapter.

5.2 Results and Discussion.

It was decided to concentrate the hydrolysis studies on the major benzaldehyde adduct (**86a**) since it was with aromatic aldehydes that good selectivities were obtained and also this compound could be easily prepared in gram quantities, as a single diastereomer, without need for column chromatography.

Many different reagents and conditions have been used to perform Pummerer type reactions and the reaction has been the subject of several recent reviews[111]. An initial reaction was tried using trifluoroacetic anhydride, buffered with pyridine in CH_2Cl_2 (the same conditions used by Hirama[108], figure 107) on the major benzaldehyde adduct (**86a**).



(86a) (86c)

Figure 112

However, only the eliminated compound (**86c**) was isolated. It would appear that trifluoroacetylation of the alcohol is occurring followed by facile elimination. Therefore a suitable protecting group for the alcohol was sought.

A number of different conditions were used to try to add a variety of protecting groups, although with limited success.

Under strongly basic conditions, which generate the alkoxide, either retro-aldol reaction or elimination occurred, figure 113.

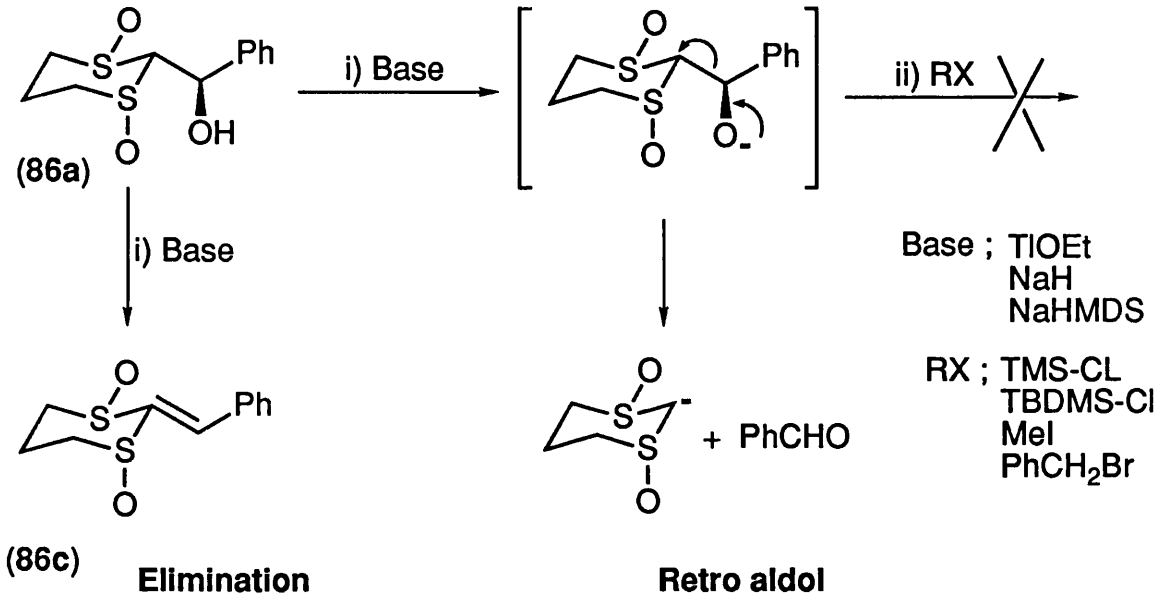


Figure 113

Attempts at trapping the alkoxide directly from an anion addition reaction were also largely unsuccessful.

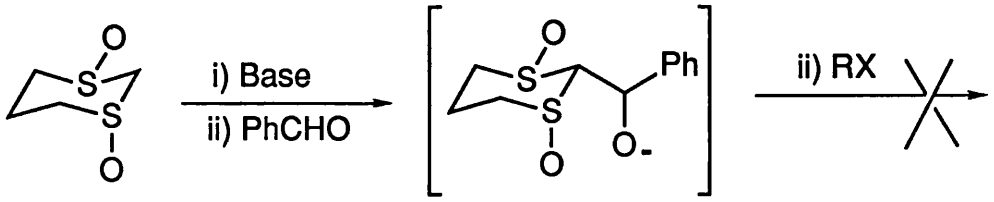
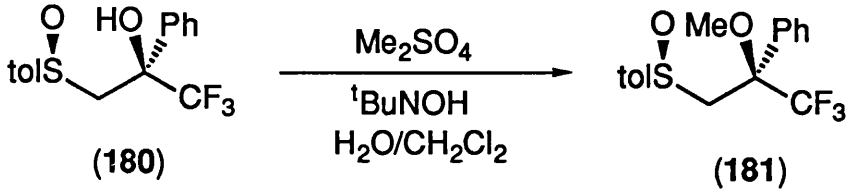


Figure 114

A small amount of the methyl ether of the benzaldehyde adduct was obtained by this method, quenching with methyl iodide, but only in low yield, and as a mixture of diastereomers.

A number of other methods were also tried, including; reaction with diazomethane and SiO_2 as catalyst[112], reaction with $TMSCHN_2$[113] and reaction with dimethylphosphite and tosic acid[114]. These were all unsuccessful.

Similar difficulties in protecting a related alcohol, (**180**) were encountered by Scolastico *et al.*[23].

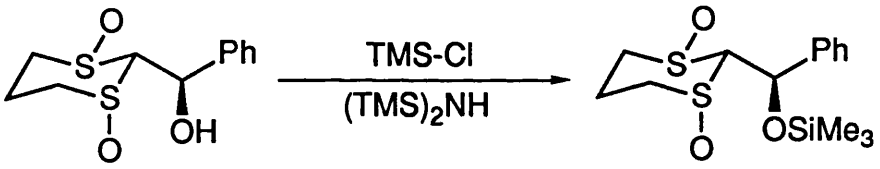


(**180**) (**181**)

Figure 115

Formation of the methyl ether (**181**) was found to be possible under phase transfer conditions, figure 115. However, these conditions were not successful when applied to (**86a**).

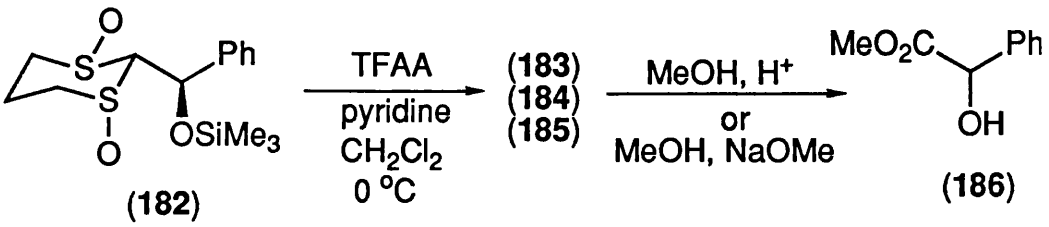
The formation of the trimethylsilyl derivative (**182**) was found to be possible by reaction of (**86a**) with a combination of trimethylsilylchloride and hexamethyldisilazane[116].



(**86a**) (**182**)

Figure 116

A Pummerer reaction with trifluoroacetic anhydride was then performed on the protected alcohol.

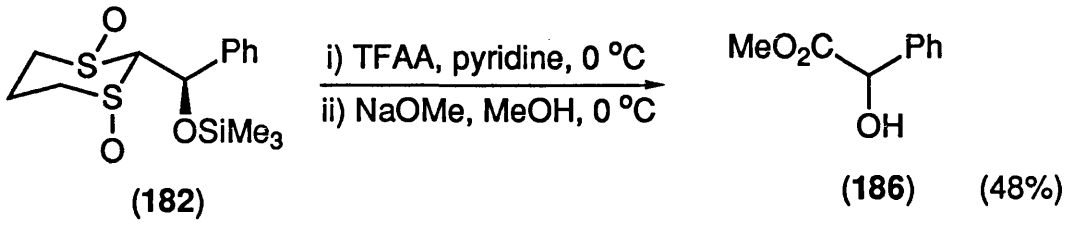


(**182**) (**186**)

Figure 117

Three unidentified products were obtained, (**183**), (**184**) and (**185**). Each of these could be transformed separately to methyl mandelate (**186**), by addition of HCl/MeOH or NaOMe/MeOH.

A "one-pot" procedure for this process was then developed. Treatment of (**182**) with trifluoroacetic anhydride in CH_2Cl_2, buffered with pyridine, followed after 15 minutes by addition of 7 equivalents of sodium methoxide in methanol led to conversion to methyl mandelate in 48% yield



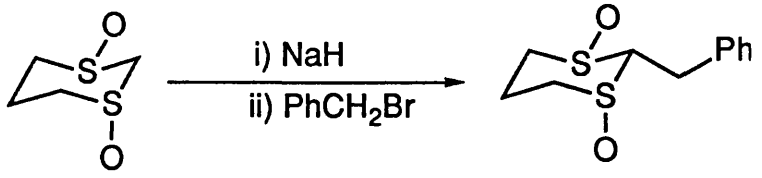
(**182**) (**186**) (48%)

Figure 118

During this sequence the trimethyl silyl group is lost. None of the isolated intermediates (**183**), (**184**) or (**185**) contained a trimethylsilyl group (apparent from their NMR spectra). Therefore hydrolysis of the protecting group must be occurring under the conditions of the Pummerer reaction. If the deprotection occurs before the Pummerer reaction is complete then trifluoroacetylation of the free alcohol and subsequent elimination could occur and this could account for the poor yield of the reaction. A more resilient protecting group was therefore sought.

During the optimization of the sequence shown in figure 118 it was decided to study a simpler model system, in which alcohol protection is not required.

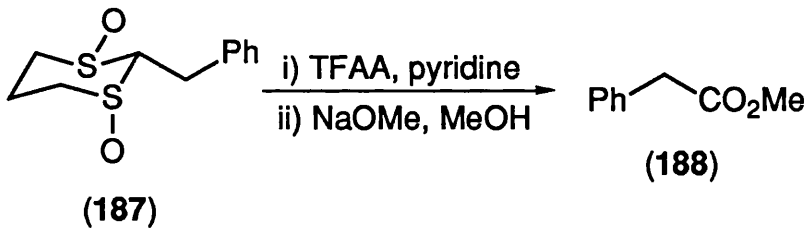
The benzylated dithiane dioxide derivative (**187**) was prepared by reaction of (**63**) with sodium hydride and benzyl bromide in DMF.



(**63**) (**187**)

Figure 119

The "one-pot" hydrolysis procedure was then carried out to give a 58% yield of methyl phenyl acetate (**188**).

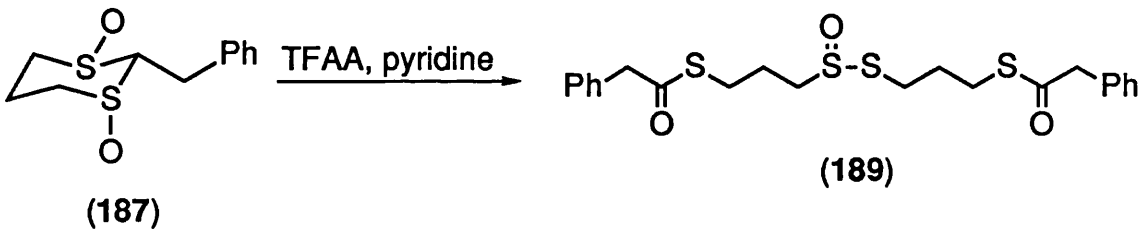


(187) (188)

Figure 120

The yield is an improvement to that obtained with the silylated alcohol (**182**), but still only modest.

The Pummerer reaction was then investigated separately in an attempt to increase the yield of the process above. Treatment of (**187**) with trifluoroacetic anhydride, followed by an aqueous work-up gave a single product (**189**), for which the structure in figure 121 has been proposed.



(187) (189)

Figure 121

The formation of (**189**) can be accounted for by the mechanism outlined in figure 122.

Trifluoroacetylation of one of the sulphoxides will generate the sulphonium ion (**190**). Attack by trifluoroacetate followed by hydrolysis upon work-up will then give the dithio ortho ester (**192**). Rearrangement, with ring opening will give rise to the thiolester/sulphenic acid (**193**). Sulphenic acids are known to spontaneously dimerize with loss of water to give thiosulphinates[117]. The dimerization of (**193**) will then give rise to the observed product (**189**).

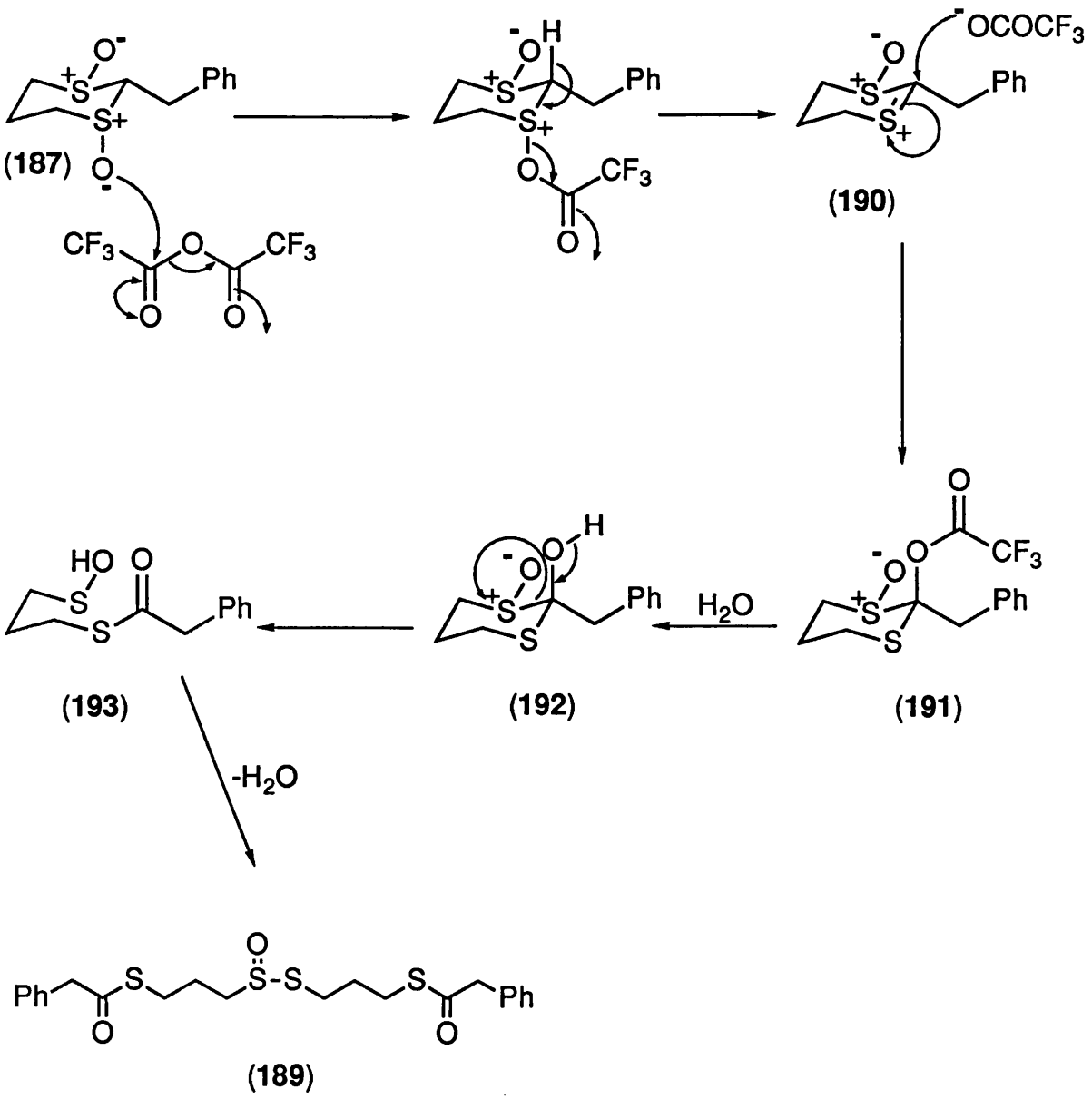


Figure 122

The ^{13}C NMR spectrum, mass spectrum and elemental analysis are all consistent with the propsed structure (see experimental section). In the J-resolved NMR spectum of (**189**) (figure 122a), two singlets for the non-equivalent benzylic protons H_a and H_h can be seen at 3.8 ppm, thus demonstrating the asymmetry of the dimer.

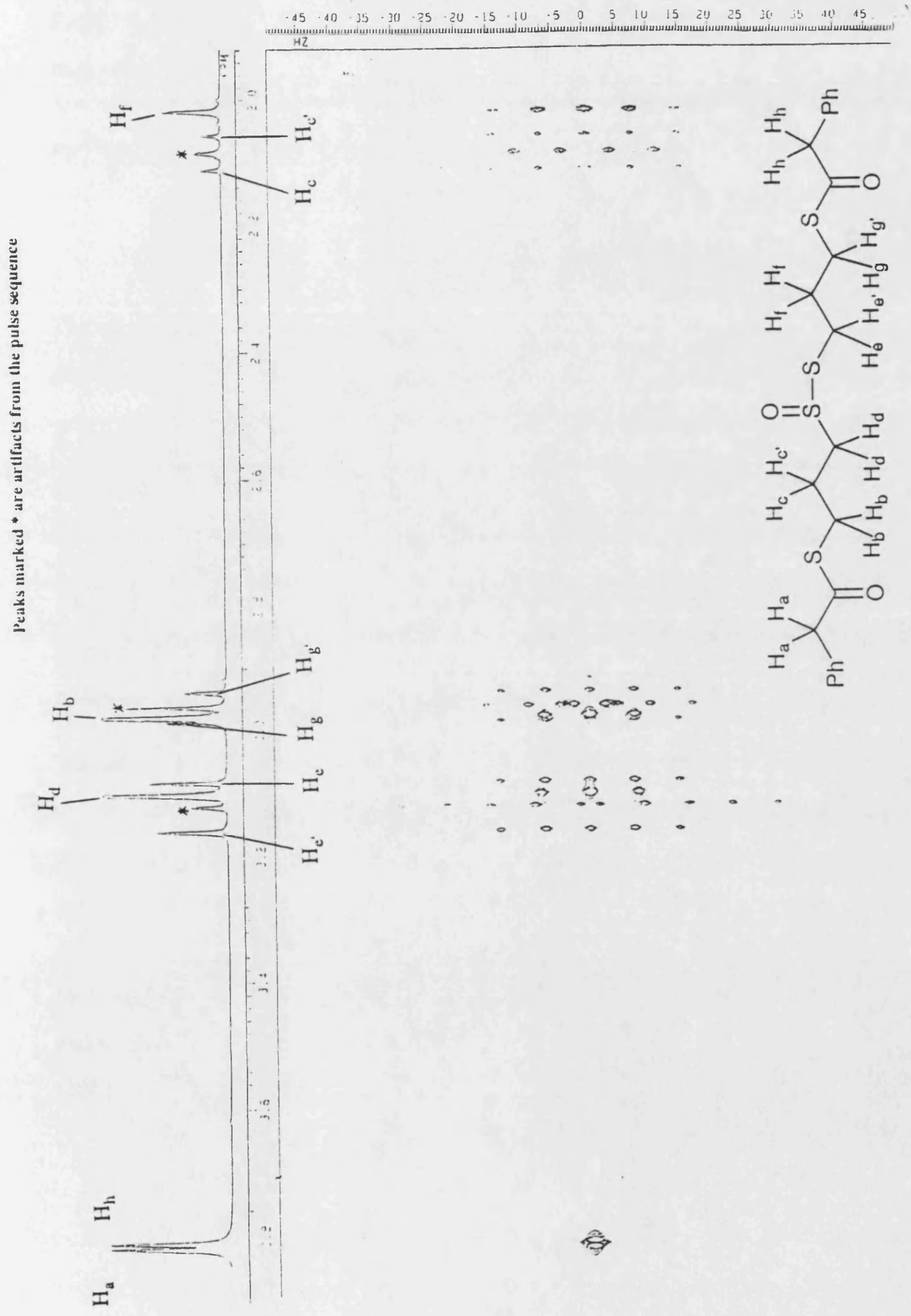
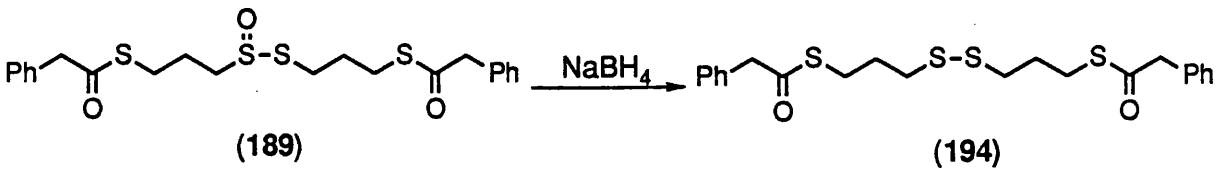

Peaks marked * are artifacts from the pulse sequence
HZ
H_a
H_h
H_d
H_b
H_f
$H_{e'}$
H_e
H_g
$H_{g'}$
H_c
$H_{c'}$
Ph
O
S

Figure 122a

Further confirmation of the structure of (**189**) was obtained by reducing the thiosulphinate to the disulphide (**194**) by treatment with sodium borohydride.



(189) (194)

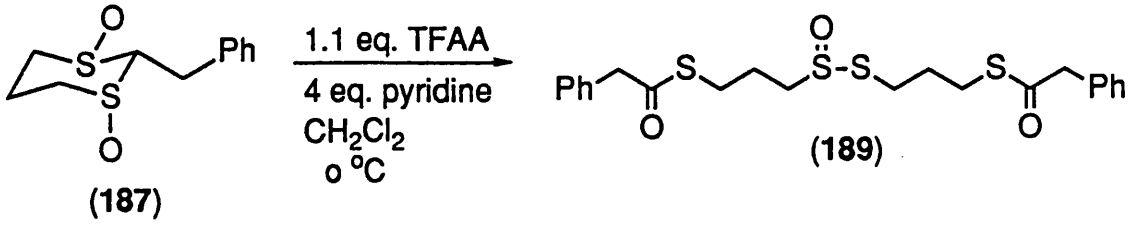
Figure 123

The ^1H NMR spectrum of (**194**) showed only a single benzylic signal indicating that the dimer becomes symmetrical upon removal of the thiosulphinate oxygen.

In order to optimize the yield of (**189**) from the Pummerer reaction, different reagents and conditions were examined.

Acetic anhydride was tried but no reaction occurred and starting material was recovered. The reaction was carried out in the absence of the pyridine buffer. However, this resulted in increased amounts of by-products being produced. The use of 2,6-lutidine in place of pyridine made no difference and a similar yield of (**189**) was obtained.

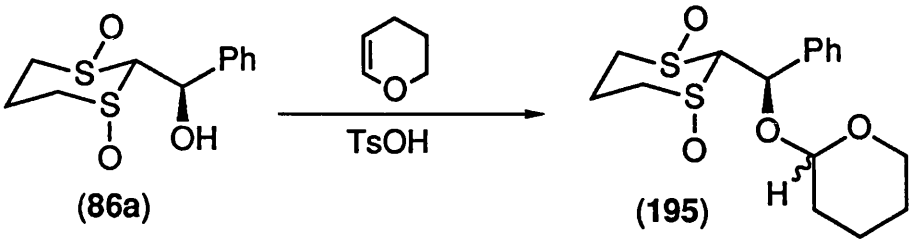
Varying the reaction temperature indicated that the reaction proceeds rapidly between -15 to 0 °C, but does not occur at -78 °C. Allowing the reaction to slowly warm up from -78 to 0 °C did not give an increased yield. The stoichiometry of trifluoroacetic anhydride was varied from 0.9 to 2.0 equivalents. It was found that 1.1 equivalents was the optimum amount, less resulted in recovered starting material and more gave increased amounts of by-products. Under the optimum conditions, 1.1 equivalents of trifluoroacetic anhydride, and 4 equivalents of pyridine in CH_2Cl_2 at 0 °C, after 15 minutes gave a 77% yield of (**189**).



(187) (189)

Figure 124

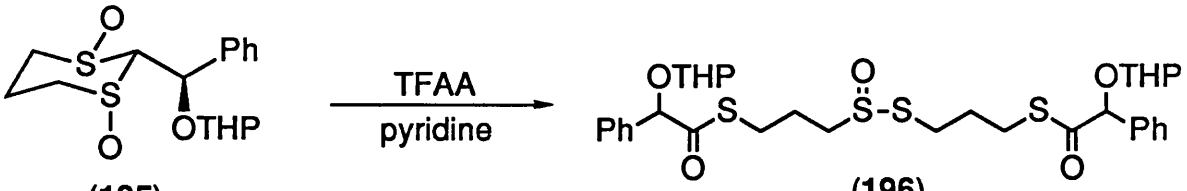
During the development of the Pummerer reaction work continued on finding a more robust protecting group for the benzaldehyde adduct (**86a**). It was found that the THP ether (**195**) could be easily prepared by treatment of (**86a**) with an excess of dihydropyran and a catalytic amount of tosic acid.



(86a) (195)

Figure 125

The Pummerer reaction, using the optimized conditions developed on the model system, was then performed on the THP ether (**195**).

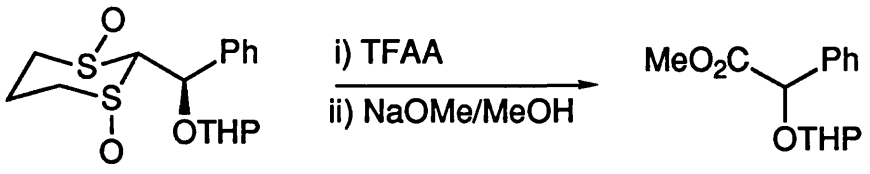


(195) (196)

Figure 126

The THP protected thiosulphinate dimer was the product from this reaction. Unlike the trimethylsilyl group the THP group withstood the Pummerer conditions. The product (**196**) was not rigorously characterised as it contains five epimeric chiral centres and is therefore potentially a mixture of sixteen diastereomers, making detailed analysis of its ^{1}H and ^{13}C NMR spectra difficult. However, there were clear analogies between the NMR spectra of (**196**) and the model compound (**189**).

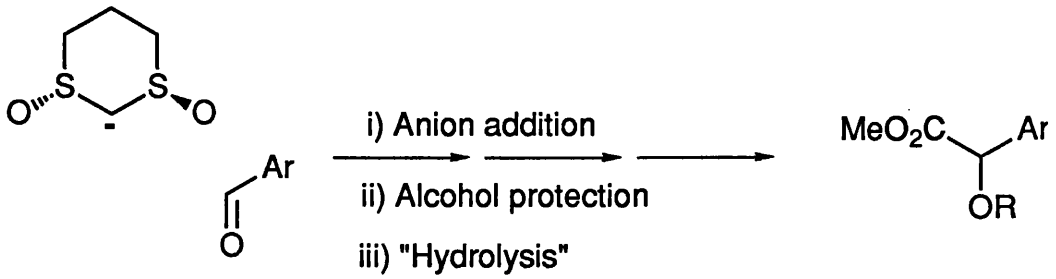
The "one-pot" procedure was then performed on (**195**) to give the THP ether of methyl mandelate (**197**), in 73% yield.



(195) (197)

Figure 127

This "hydrolysis" procedure oxidises the C-2 carbon of the dithiane dioxide moiety from the aldehyde to the carboxylic acid oxidation level.



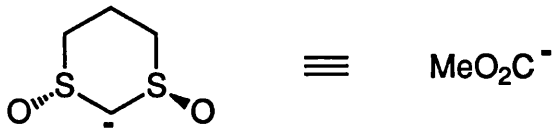


Figure 128

The dithiane dioxide anion therefore represents a chiral hydroxy carbonyl anion equivalent when this hydrolysis protocol is used.

All the reactions described so far have been performed using racemic compounds. So although good diastereoselectivities can be obtained in the anion additions to aromatic aldehydes,the absolute configuration of the newly created chiral centre is not controlled and the hydrolysis product (**197**) is racemic. It must be demonstrated that starting from homochiral dithiane dioxide, (**63**) will lead to the synthesis of homochiral α-hydroxy carbonyl compounds, such as (**197**), and that the optical integrity at the α-hydroxy chiral centre is maintained during the hydrolysis procedure. In order to do this the synthesis of (**197**) was repeated, starting with (+)-(RR)-(**63**).[e]

[e] Homochiral (+)-(RR)-(**63**) was prepared as outlined in chapter 2.

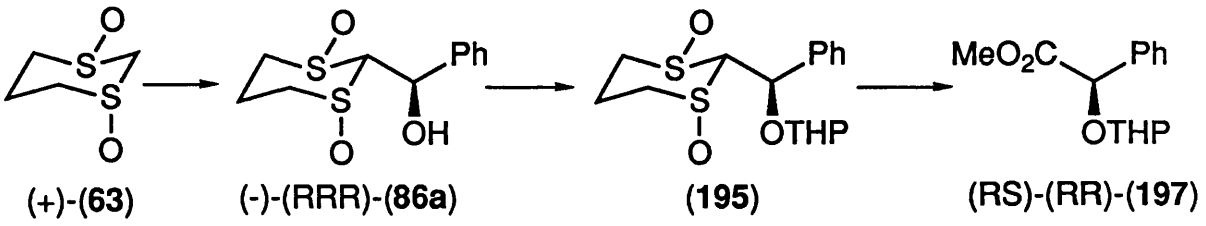


Figure 129

Using the established conditions the benzaldehyde adduct (-)-(RRR)-(**86a**) was prepared, protected and hydrolysed to give optically active (RS)-(RR)-(**197**) (although as a mixture of diastereomers, due to the epimeric chiral centre of the THP group). The product was then examined by chiral shift NMR to determine the optical purity at the α-hydroxy chiral centre.

The chiral shift NMR spectra obtained with the racemate (+/-)-(**197**) are shown in figure 130a. Spectrum A is from just (+/-)-(**197**). Two singlets for the benzylic proton H_a can be seen at 5.2-5.4 ppm, one from each of the two diastereomers. Spectrum B is from (+/-)-(**197**) plus 2,2,2-trifluoro-1-(9-anthryl)ethanol, (TFAE), the Pirkle shift reagent[118]. The benzyl singlets have been split and two peaks are seen for each diastereomer. This demonstrated that a suitable peak could be resolved into the two enantiomers. The optically active material was then examined. Figure 130b shows the spectra obtained with (RS)-(RR)-(**197**). A small peak for the minor enantiomer of each diastereomer can be seen and the optical purity at the benzylic chiral centre was determined as 90% e.e.

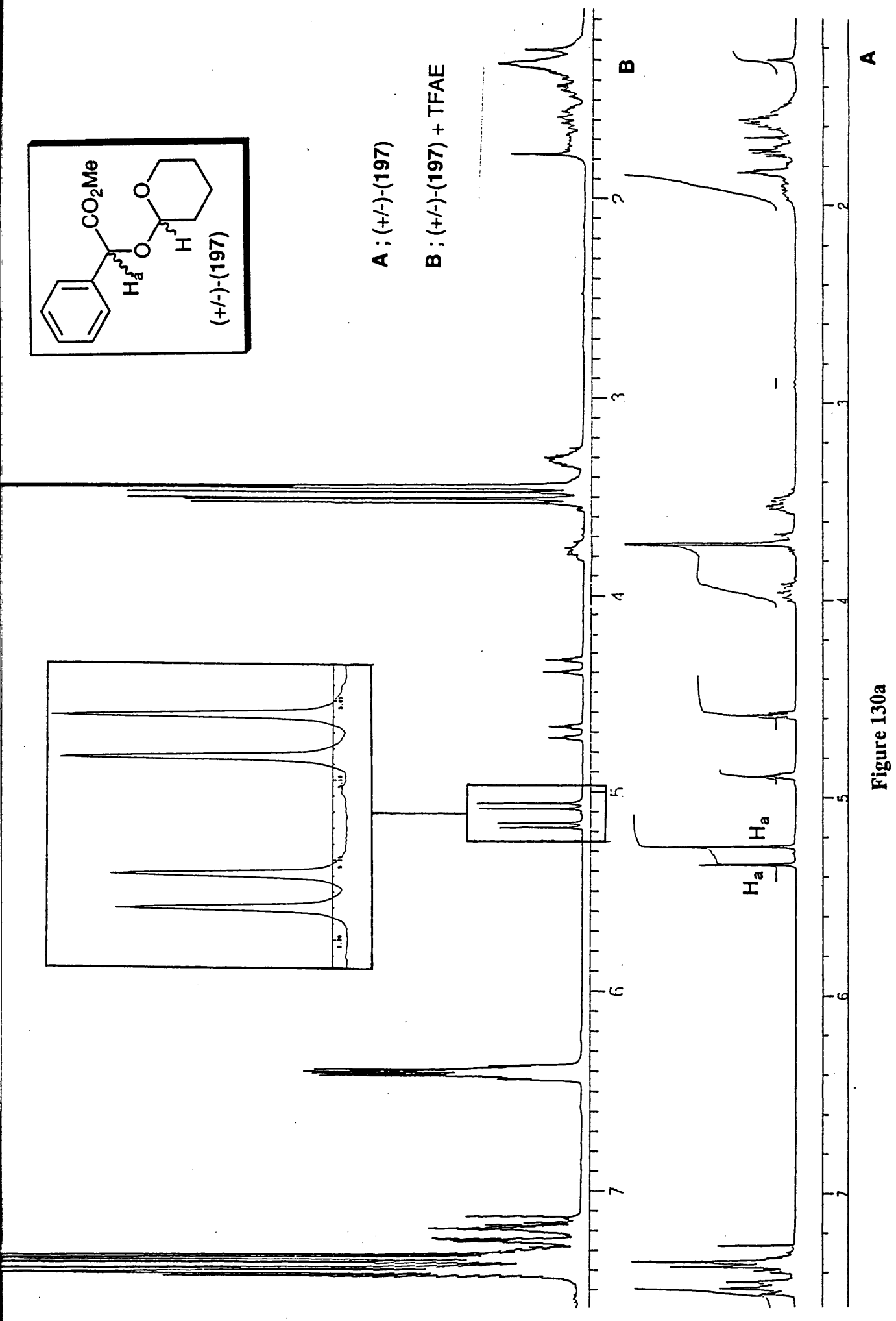


Figure 130a

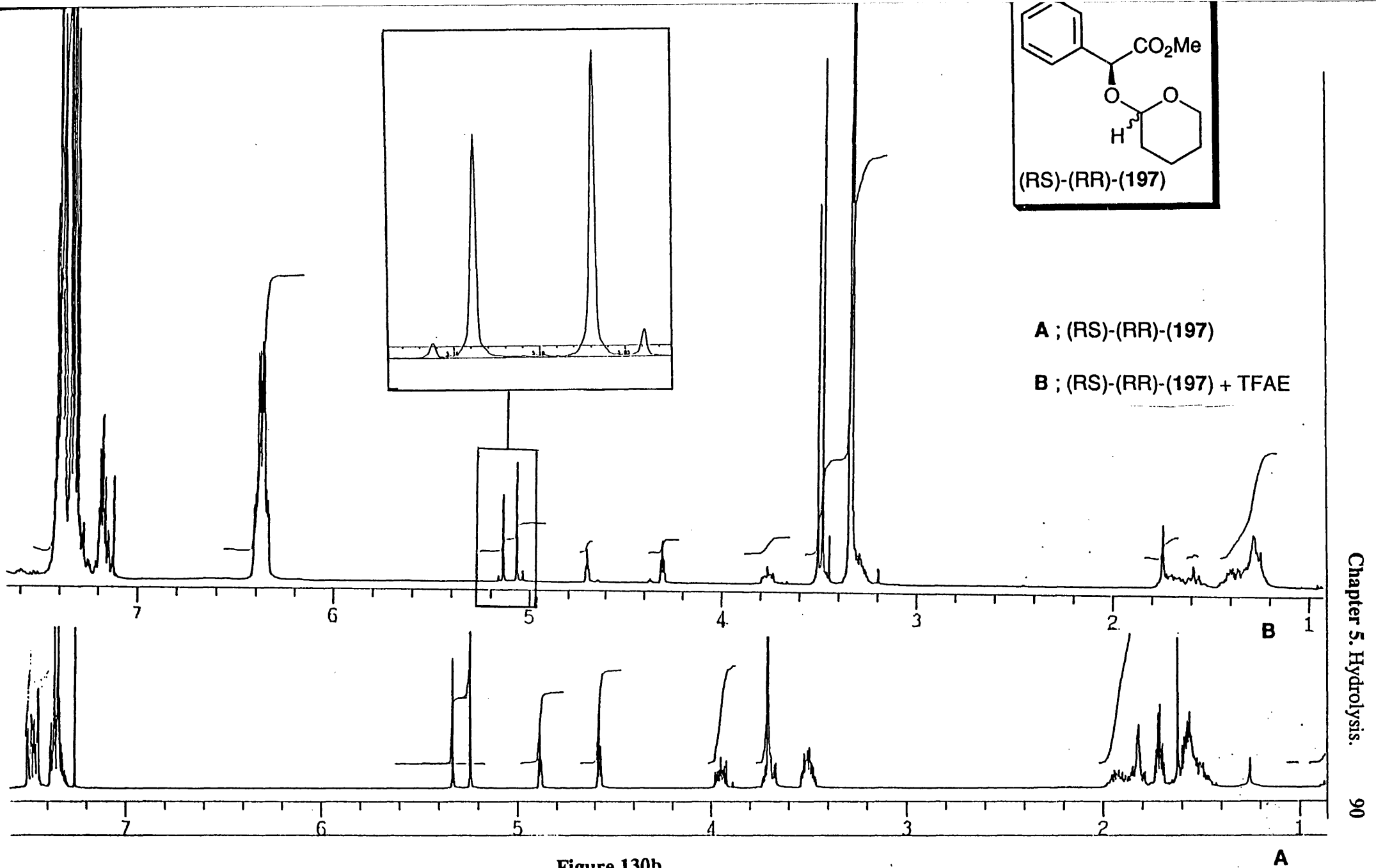

CO2Me
O
O
H
(RS)-(RR)-(197)
A ; (RS)-(RR)-(197)
B ; (RS)-(RR)-(197) + TFAE
7
6
5
4
3
2
1
B
7
6
5
4
3
2
1
A

Figure 130b

Therefore at some point during the hydrolysis a small degree of racemization had occurred. There is literature precedent to suggest that racemization of chiral centres alpha to sulphoxides during Pummerer reactions does not occur, (see 5.1). It was assumed therefore, that the observed racemization of (RR)-(RS)-(**197**) was due to the use of sodium methoxide, which may abstract the acidic proton at the benzylic chiral centre.

Other, non-basic transformations of thiolesters were therefore investigated. These are discussed below under several general headings.

Reactions with alcohols and amines.

Thiolesters can be considered as activated esters, and the possibility of forming amides directly, by reaction with an amine was investigated. The thiosulphinate dimer (**196**) was reacted with benzylamine and cyclohexylamine. Several different solvents were used; acetone, pyridine, DMF, acetonitrile and methanol. Of these, methanol gave the best yields.

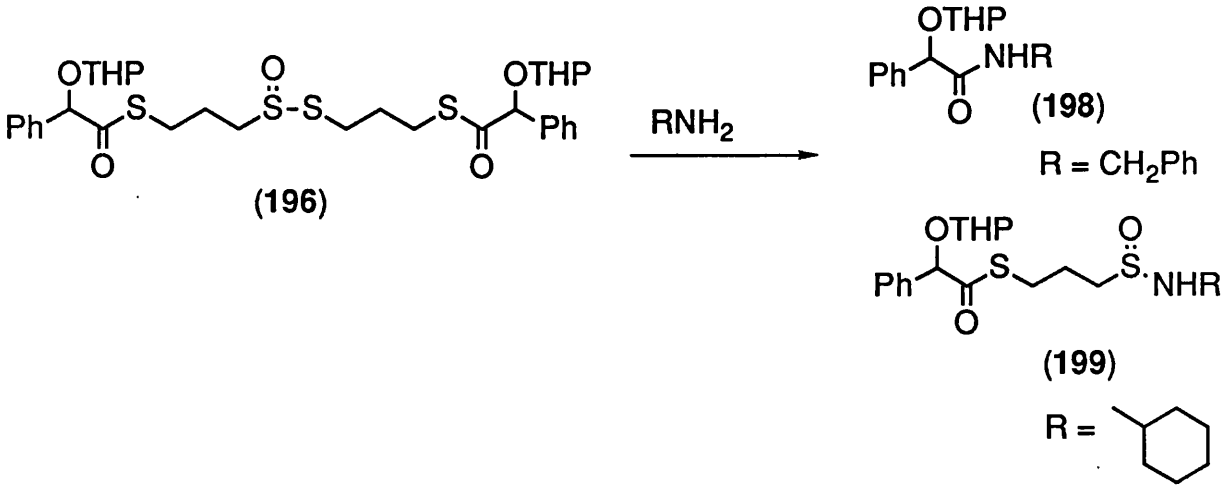


Figure 131

In the reaction with benzylamine the desired amide (**198**) was obtained after several days reaction at room temperature. However, despite many attempts, the reaction with cyclohexylamine gave only the sulphinamide (**199**).

Presumably the secondary amine is not sufficiently nucleophilic to react at the thiolester and only the relatively weak S-S bond of the thiosulphinate is cleaved.

There are several literature reports of the use of silver, mercury and copper salts as activating agents in the reaction of thiolesters with nucleophiles[119-122]. The use of thiophilic transition metals was investigated in the reactions of (**196**) with alcohols and amines. A number of different metal salts were tried; $AgOCOCF_3$, $Hg(OCOCF_3)_2$, AgSCN, AgOCOPh, $AgOCOCH_3$, $AgSO_3ptol$, $AgClO_4$, $Cu(SO_3CF_3)_2$ and ZnI_2, in combination with cyclohexanol or cyclohexylamine.

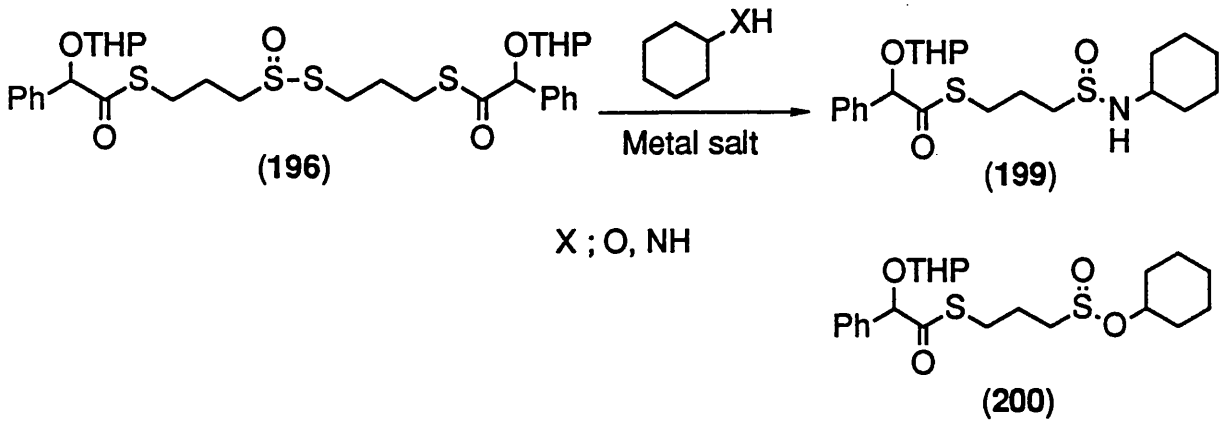
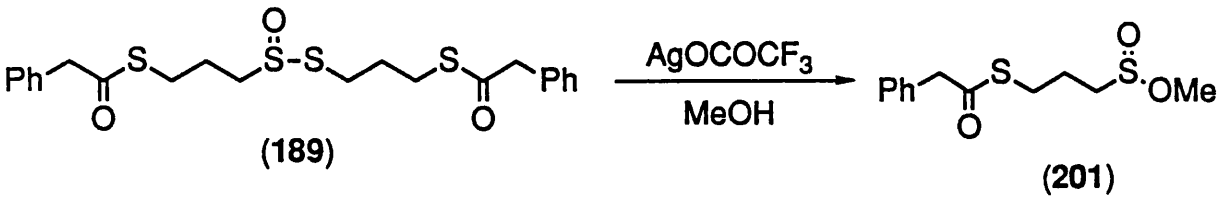


Figure 132

However, in all cases (except for reactions with Cu(II) or Zn(II) salts, where only starting material was recovered) the product of the reaction was either the sulphinamide (**199**) or the sulphinyl ester (**200**).

Silver trifluoroacetate, $AgOCOCF_3$, was found to be the most effective reagent in these transformations, but despite many variations to the reaction conditions, such as stoichiometry of reagents, temperature and pH of the reaction mixture the only products obtained were (**199**) and (**200**).

To eliminate the possibility that reaction at the thiolester is prevented due to steric interactions, the reaction was tried with methanol and the model compound (**189**), which has no substituent alpha to the thiolester.

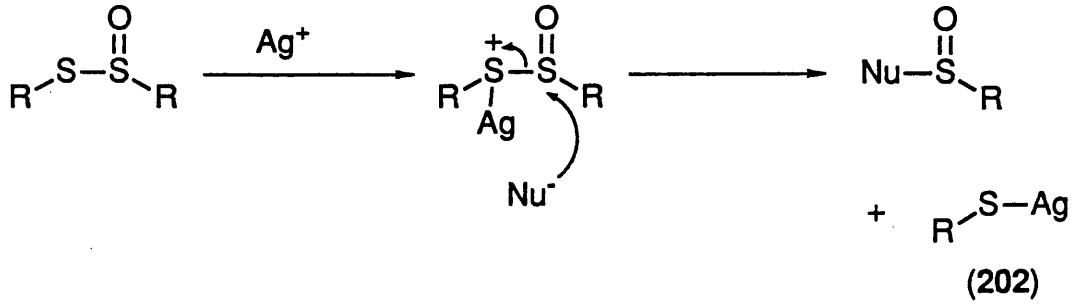


(189) (201)

Figure 133

However, again reaction only occurred at the thiosulphinate and not at the thiolester. This approach was then abandoned

The reason for the failure of these reactions is not clear. Literature precedent would suggest that the reaction of thiolesters with alcohols and amines in the presence of silver salts should be facile, however in the reactions with (**189**) and (**196**) only the more reactive thiosulphinate is affected. It is interesting to note that the sulphinyl ester or the sulphinamide are the only isolated products from the reactions. This represents only one half of the substrate dimer.



(202)

Figure 134

Presumably the other half forms a silver thiolate (**202**) which is lost during chromatography.

Oxidative Reactions.

If a thiolester is oxidised in the presence of a nucleophile then nucleophilic attack of the oxidised species should readily occur .

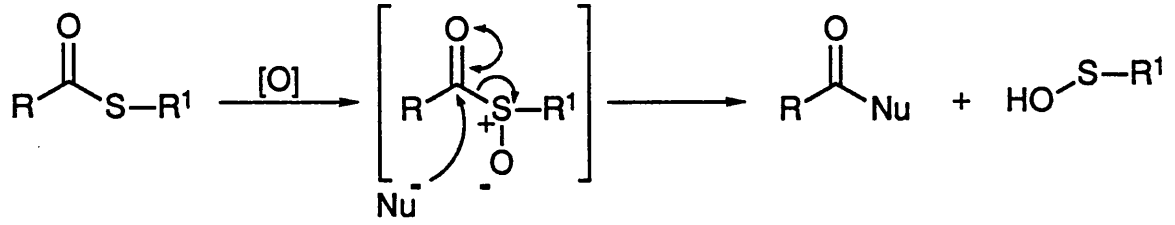


Figure 135

A number of reactions employing this approach were investigated. The simpler model compound (**189**) was used as a test substrate in most cases. Using conditions reported by Minato[123] for the transesterification of thiolesters, (**189**) was oxidised with iodine in the presence of methanol.

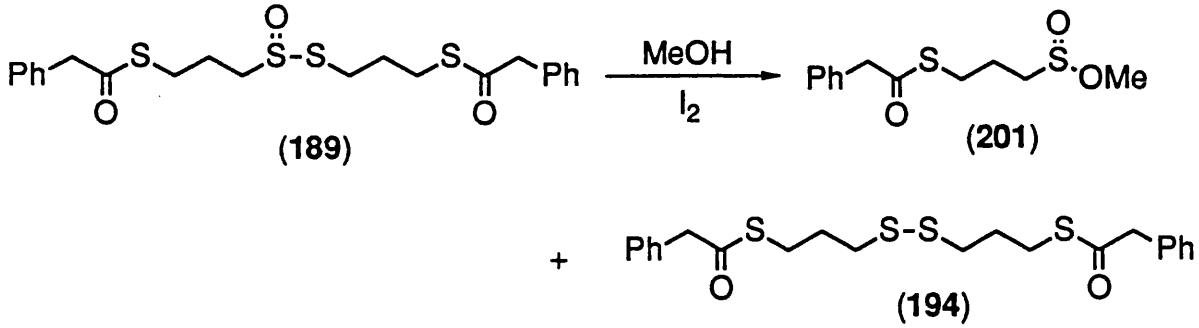


Figure 136

The rapid reaction gave rise to two new products, the sulphinyl ester (**201**) and the disulphide dimer (**194**). Presumably reaction occurs at the thiosulphinate to give the sulphinyl ester (**201**) and the thiol (**203**). Oxidation of this thiol will give rise to the disulphide (**194**).

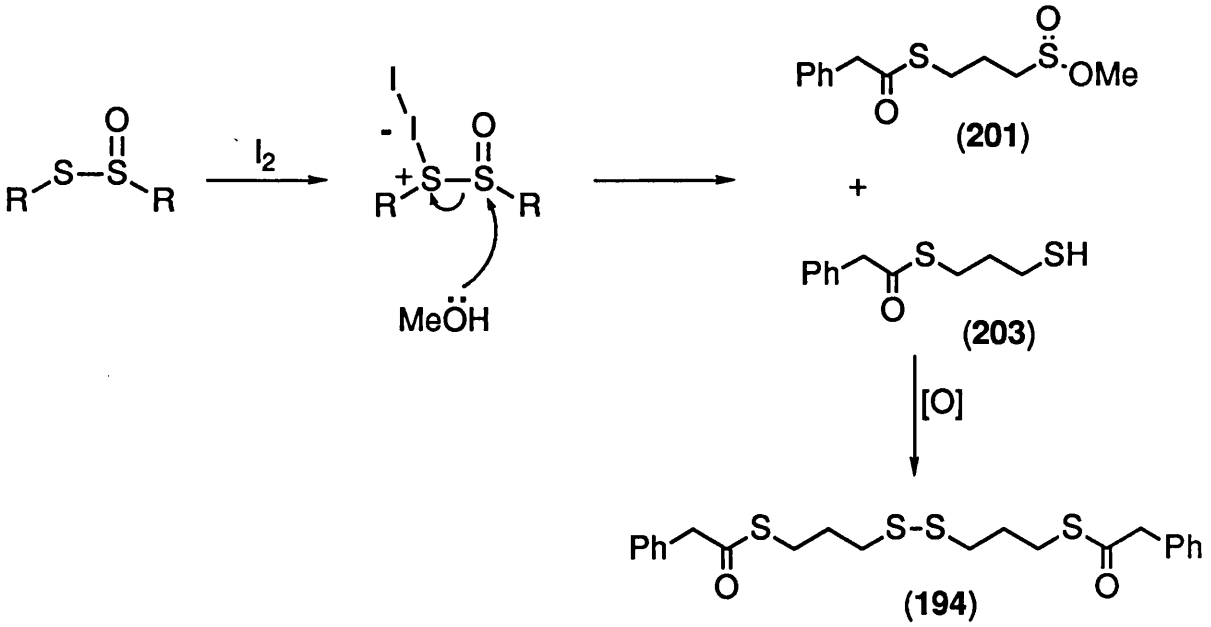


Figure 137

Minato observed the transesterification of *S*-phenyl thioacetate with only a catalytic amount of iodine. However, despite using several equivalents neither of the thiolesters (**201**) and (**194**) reacted further.

A stronger oxidant was therefore employed. The reaction of (**189**) with MCPBA in methanol gave the desired product, methyl ester (**188**) in 51% yield.

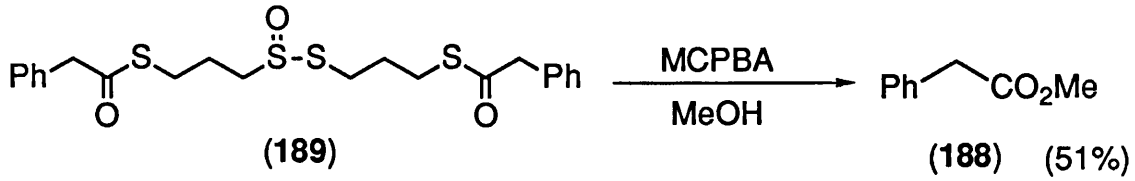


Figure 138

The feasibility of extending this reaction to a "one-pot" procedure was examined. However, Pummerer reaction followed by addition of MCPBA and methanol gave the product in only 15% yield.

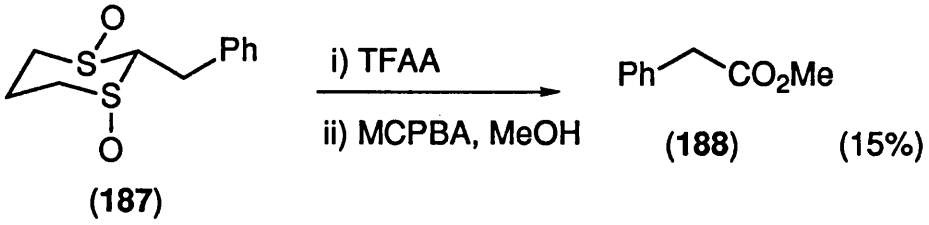


Figure 139

The oxidative hydrolysis of (**189**) could be achieved by reaction with lithium hydroxide and hydrogen peroxide to give phenyl acetic acid, (**204**).

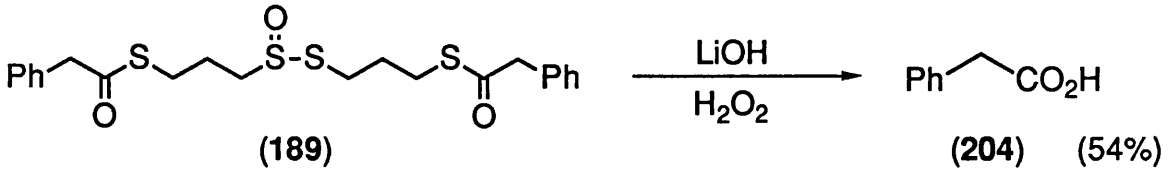


Figure 140

These conditions were also tried on the protected α-hydroxy compound (**196**).

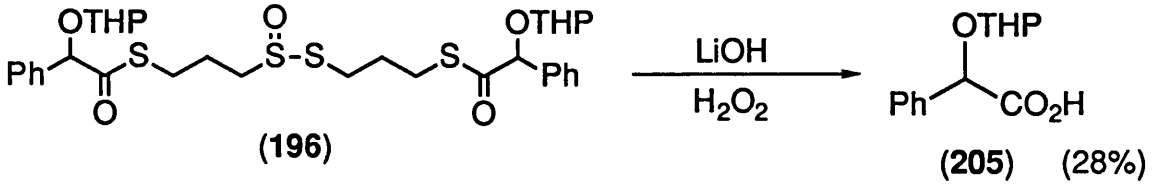


Figure 141

However only a poor yield of the acid was obtained.

The use of OXONE in aqueous methanol was investigated. Reaction with (**189**) gave phenyl acetic acid (**204**) in almost quantitative yield.

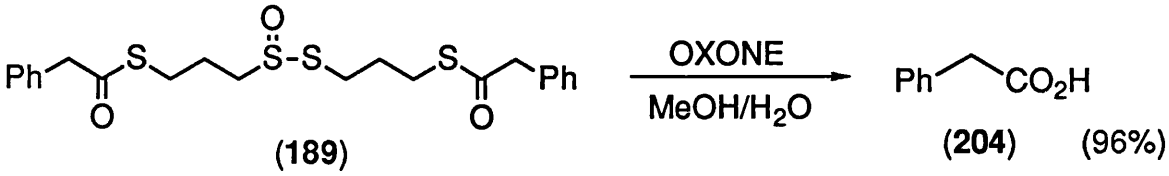
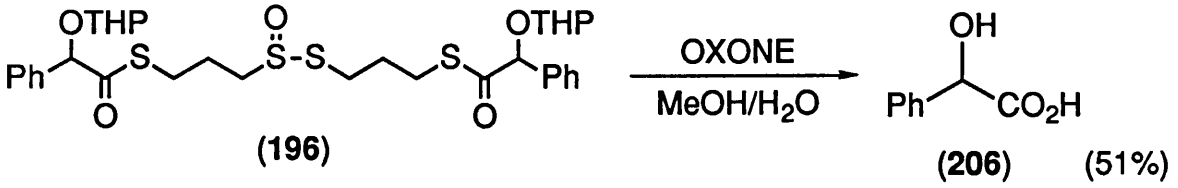


Figure 142

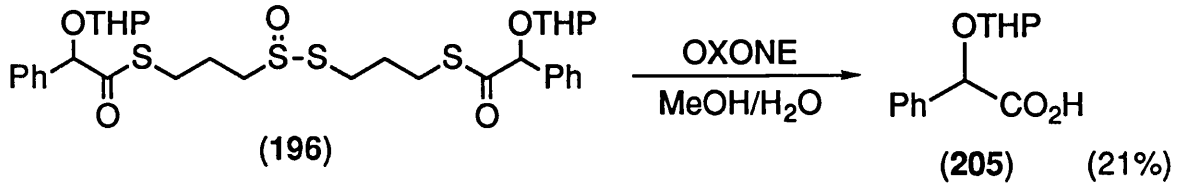
However, when applied to the α-hydroxy compound (**196**) mandelic acid (**206**) was produced in only modest yield.



(196) (206) (51%)

Figure 143

The reduced yield of mandelic acid (**206**) compared to that of phenyl acetic acid (**204**) is due to the problem in isolating the product from the reaction mixture. Mandelic acid is highly polar and can only be partially extracted during the aqueous work-up. The THP group is lost during the reaction due to the acidity of the OXONE reagent. It was therefore thought that adjusting the pH of the reaction would prevent the THP hydrolysis and hence give a less polar product which could be more readily isolated. The reaction was repeated using a range of stoichiometries of $NaHCO_3$, to give THP protected mandelic acid (**205**). However, when the pH of the reaction mixture is raised sufficiently to prevent loss of the THP group the reactivity of OXONE is dramatically reduced and the highest yield from these reactions was only 21%.



(196) (205) (21%)

Figure 144

Thiolester Exchange.

The failure or only limited success of the reactions tried on the thiolester/thiosulphinate dimers (**189**) and (**196**) was disappointing. The thiolester functionality is potentially very versatile and to enable easier investigations of possible reactions of the thiolester it was thought preferable to have a substrate that did not contain the more reactive thiosulphinate group. The possibility of a thiolester exchange was therefore investigated.

Initial attempts concentrated on forming a 2-pyridyl thiolester, since this grouping is particularly versatile and has been used in peptide bond formation[124] and in the preparation

of ketones in the reactions with Grignard reagents[125] in addition to standard thiolester reactions.

Using the model system, (**189**) was treated with a mixture of 2-mercaptopyridine and sodium methoxide to generate an excess of the thiolate *in situ.*

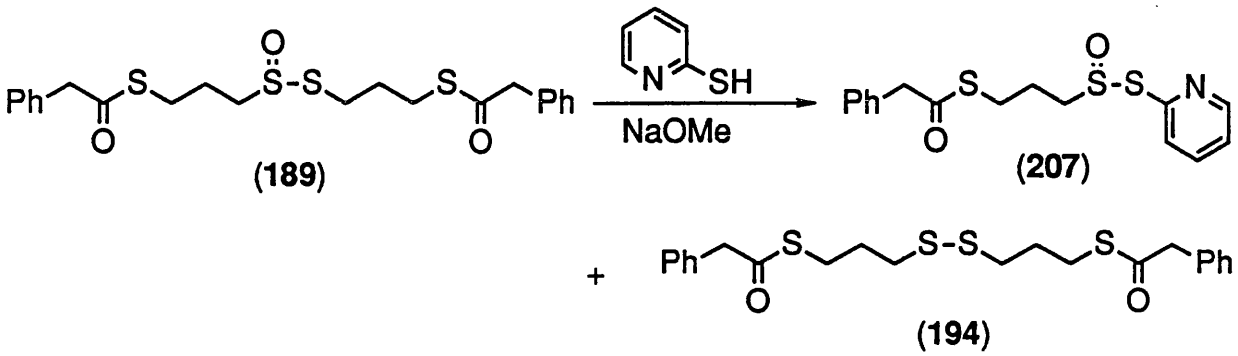


Figure 145

Two new products were generated, the 2-pyridyl thiosulphinate (**207**) and the disulphide (**194**). Again it appears that reaction only occurs at the more reactive thiosulphinate group. The formation of (**194**) is due to aerial oxidation of the initially formed thiol during work-up and purification.

An analogous reaction was carried out with sodium ethanethiolate in ethanethiol.

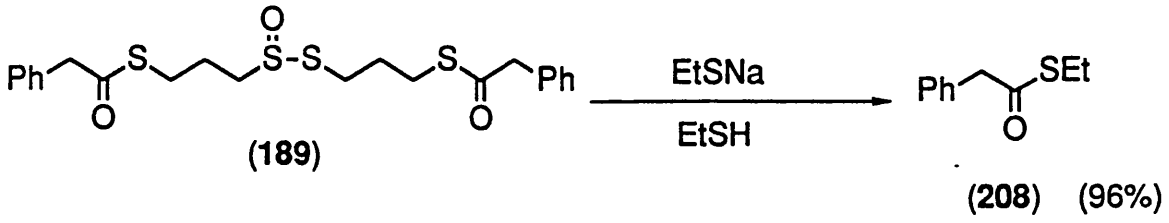


Figure 146

The ethylthio ester (**208**) was produced in near quantitative yield. This reaction was also examined in a number of solvents. In methanol and CH_2Cl_2 the reaction rate was considerably slower compared to that in neat ethanethiol while in THF it was slightly faster. When applied to (**196**) these conditions also gave an excellent yield of the protected α-hydroxy ethanethiol (**209**).

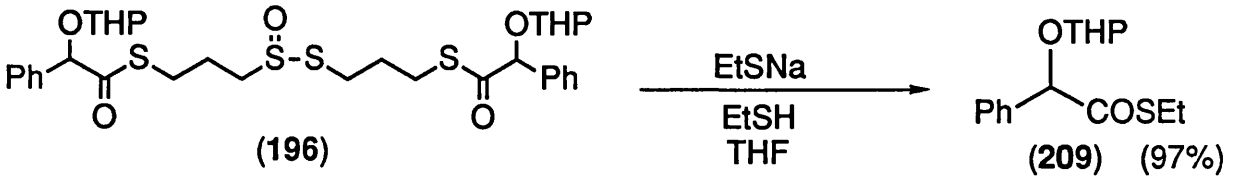


Figure 147

It was possible to use this reaction in a "one-pot" hydrolysis to give (**209**) in 74% yield from the dithiane (**195**).

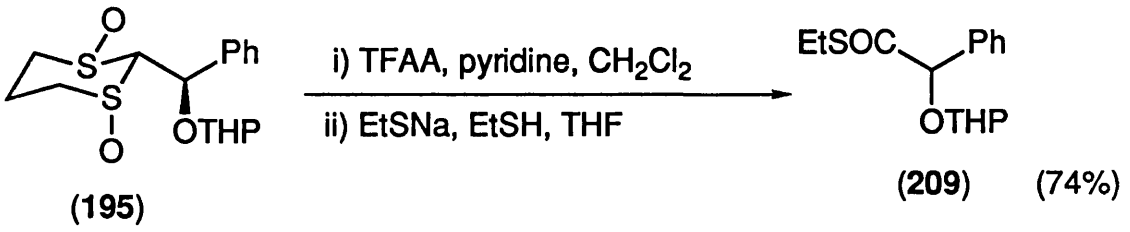


Figure 148

In order to establish that this reaction could be used without any racemization of the hydroxy chiral centre the reaction was carried out on optically pure material.

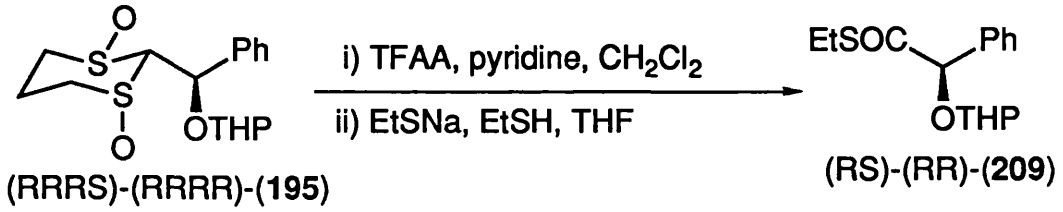


Figure 149

Chiral shift analysis of the product (RR)-(RS)-(**209**) was not successful, however due to the close proximity of the signals from the two diastereomers. The THP group was therefore removed to give the chiral alcohol (-)-(R)-(**210**).

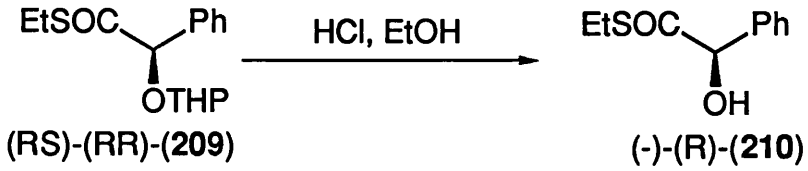


Figure 150

The racemate (+/-)-(**210**) was also prepared from (+/-)-(**209**). Addition of the chiral shift reagent TFAE, resolved the benzylic singlet of the racemate, figure 151a. Expansions of the

benzylic peak from the spectra obtained with optically active material are shown in figure 151b. Spectra A was obtained with (-)-(**210**) and TFAE. Essentially only a single peak was seen, with a very small shoulder which may be due to the minor enantiomer. To ensure resolution of the enantiomers was being achieved, the sample was spiked with small amounts of the racemate (+/-)-(**210**) to give the spectra B and C. The small shoulder seen in spectrum A increased upon addition of the racemate, indicating that indeed this was due to the minor enantiomer. Integration of the signals indicated that the optical purity of (-)-(**210**) was >95%e.e.

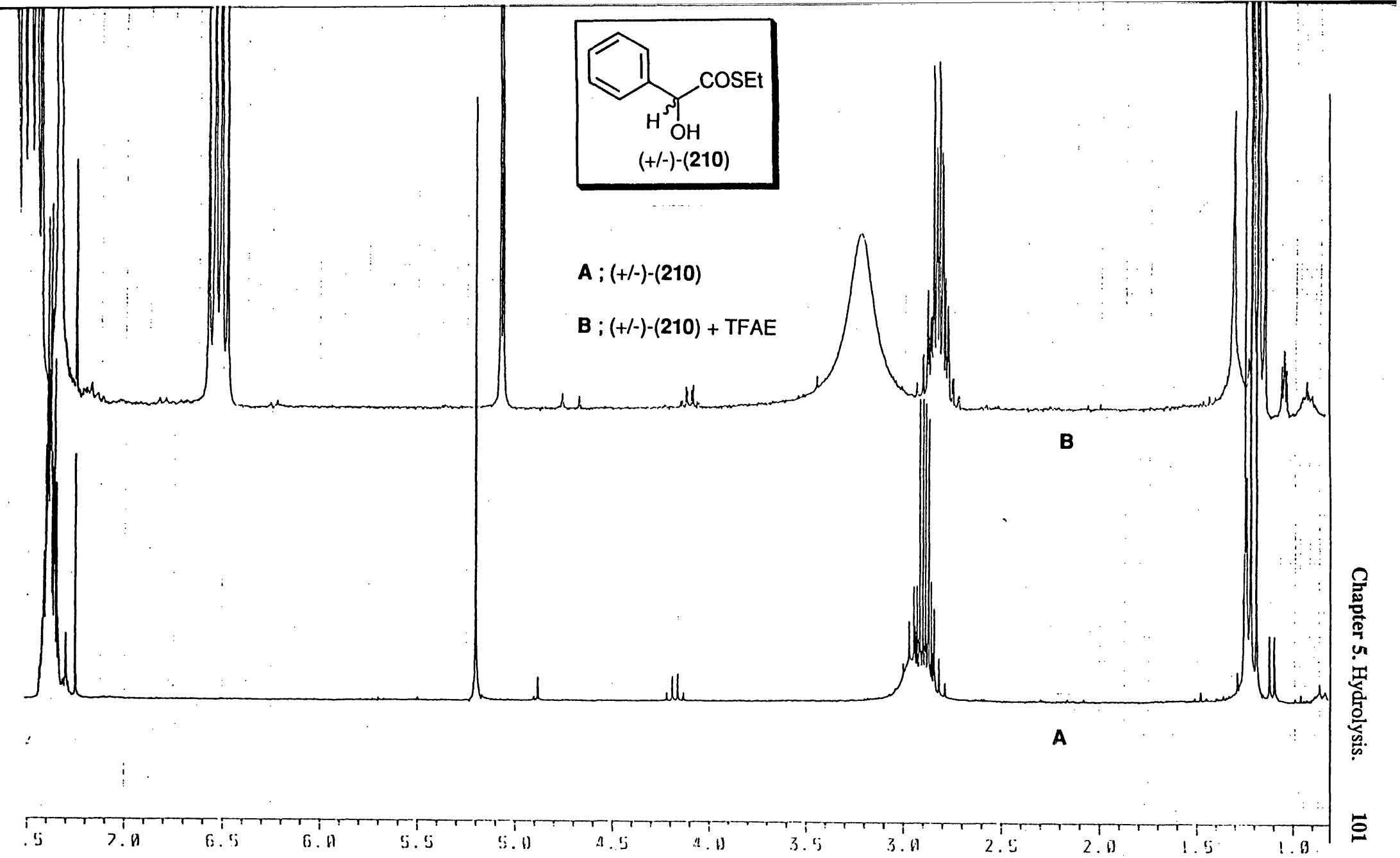

COSEt
H
OH
(+/-)-(210)
A ; (+/-)-(210)
B ; (+/-)-(210) + TFAE
B
A
.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

Figure 151a

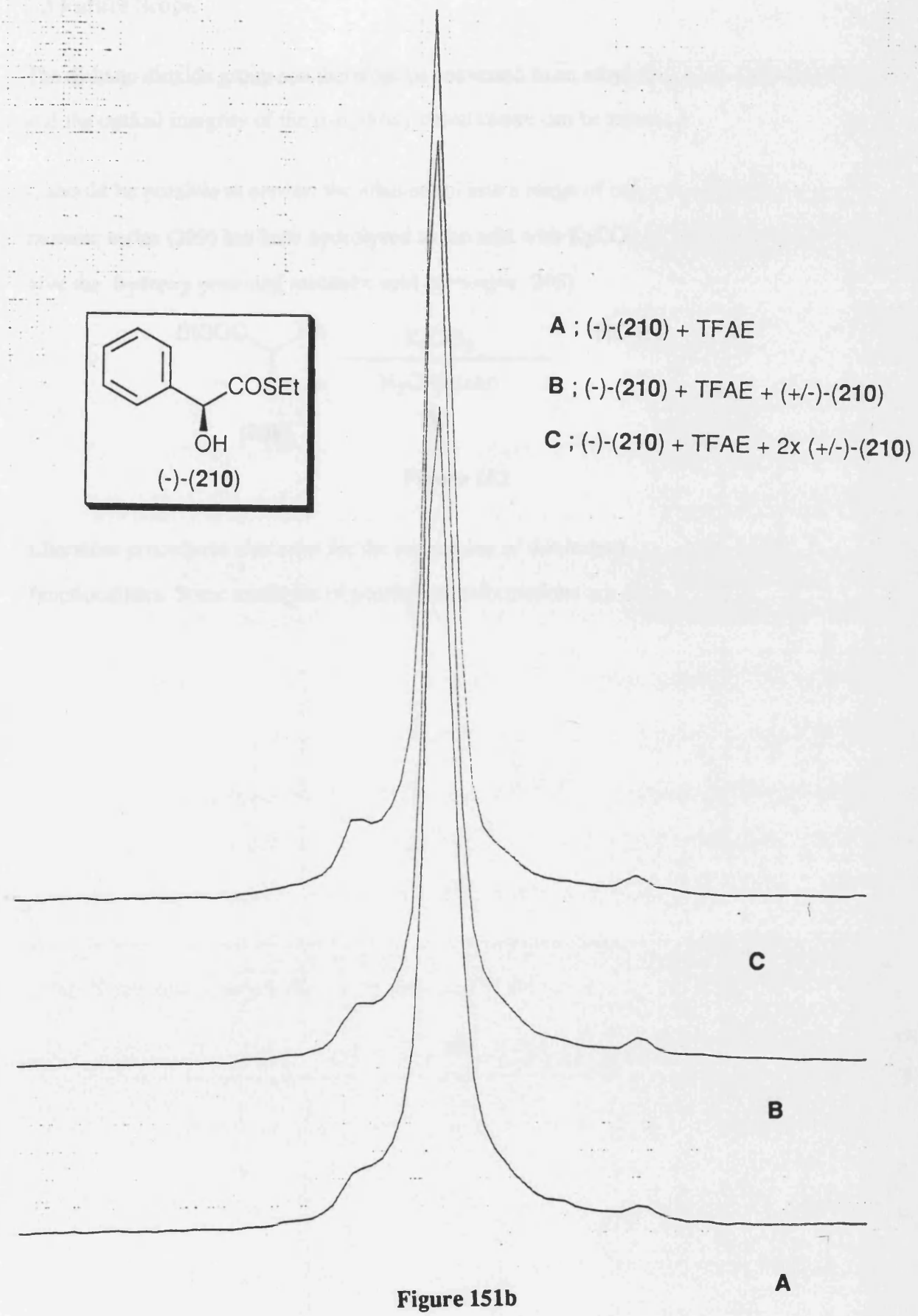


Figure 151b

5.3 Future Scope.

The dithane dioxide group can therefore be converted to an ethyl thiolester in good yield, and the optical integrity of the α-hydroxy chiral centre can be retained.

It should be possible to convert the ethanethiol into a range of other functionalities. In the racemic series (**209**) has been hydrolysed to the acid with K_2CO_3 in water/dioxan[108], to give the hydroxy protected mandelic acid derivative (**205**).

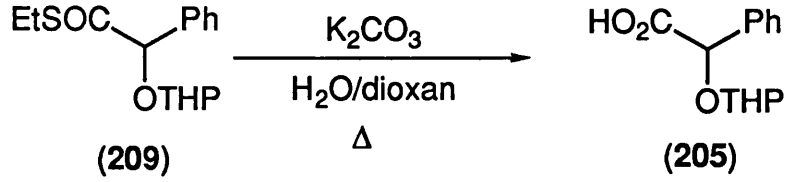


Figure 152

Literature procedures also exist for the conversion of thiolesters into many other functionalities. Some examples of possible transformations are shown in figure 153.

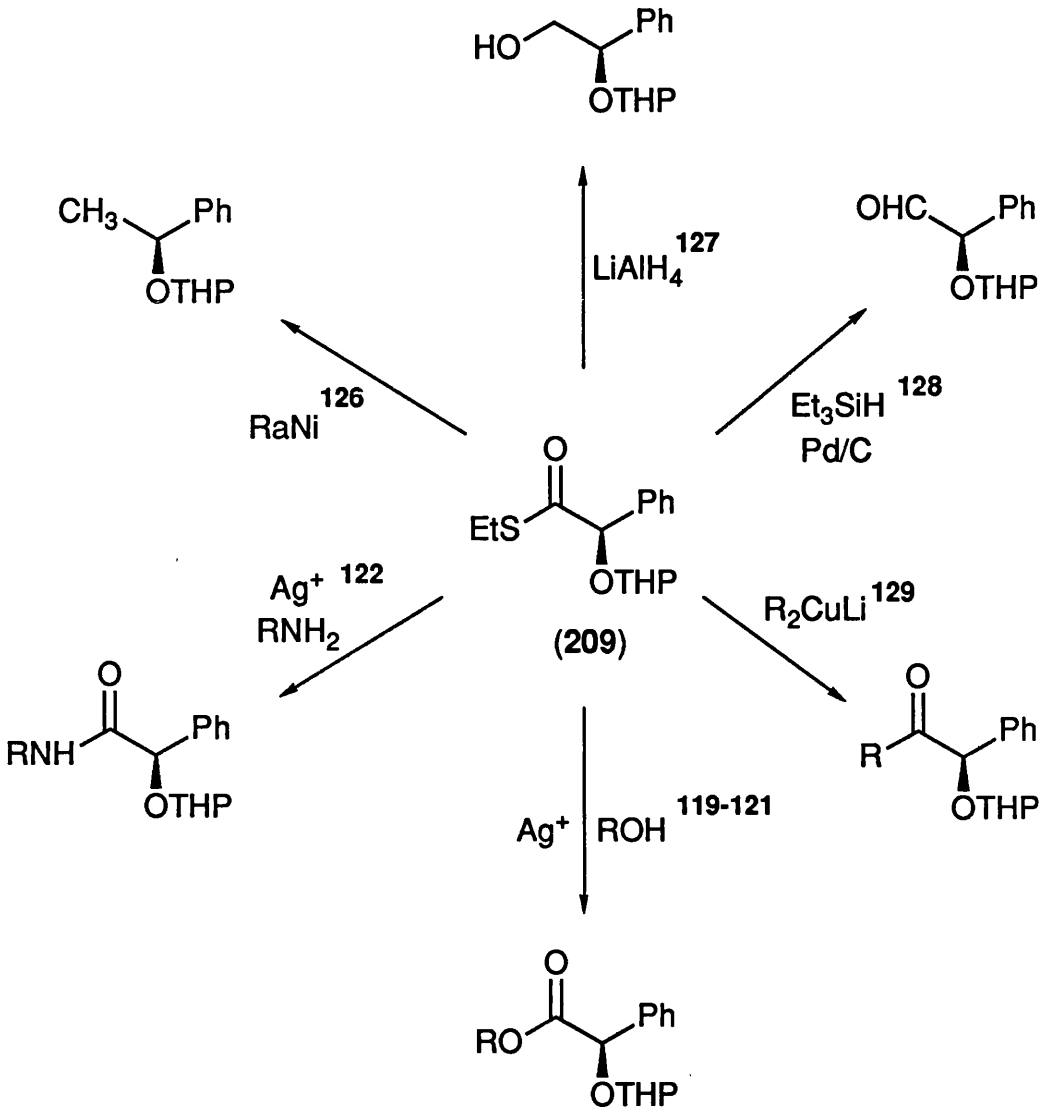


Figure 153

Therefore, using this methodology it should be possible to synthesise, in optically pure form, molecules of general structure (**212**), from aromatic aldehydes. The nature of the group X can be determined during the final step of the sequence.

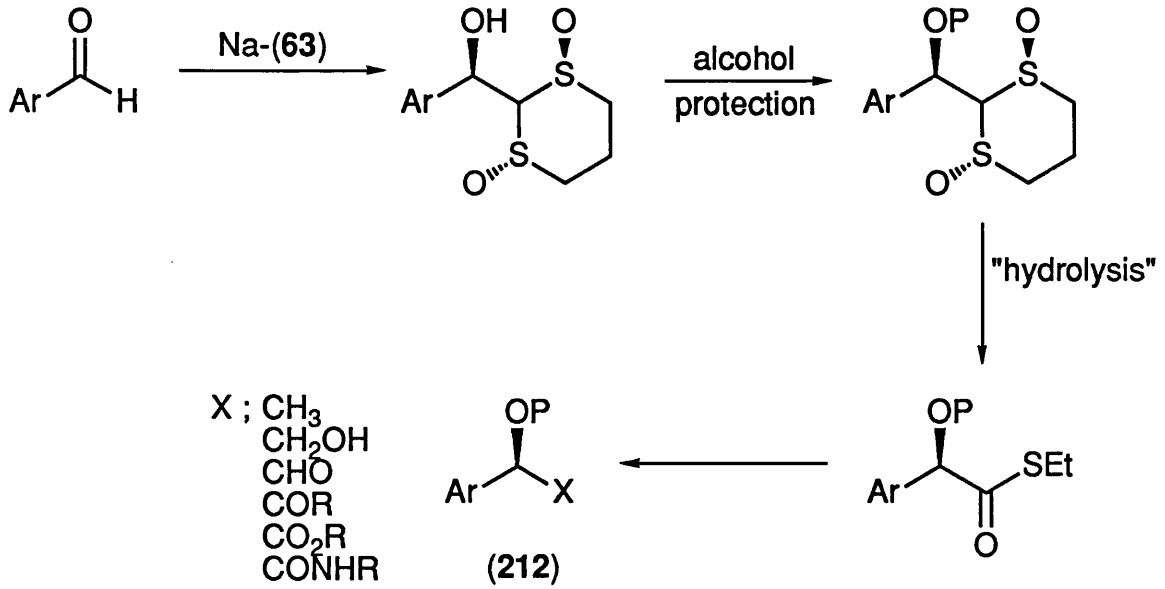


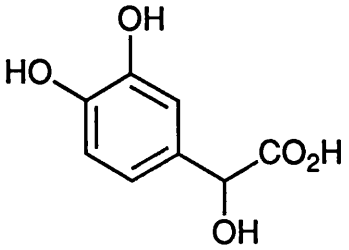
Figure 154

Thus, dithiane dioxide (**63**) is potentially a very versatile chiral X^- anion equivalent for all the groups X listed in figure 154.

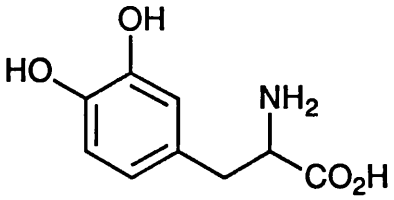
CHAPTER 6. TOWARDS AN ASYMMETRIC SYNTHESIS OF 3,4-DIHYDROXYMANDELIC ACID.

6.1 Introduction.

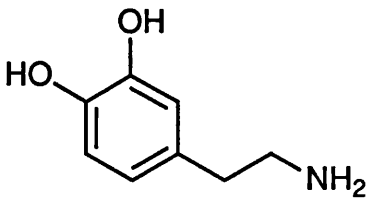
3,4-Dihydroxymandelic acid (**213**) is a naturally occurring compound. Structurally it is similar to catecholamines, *e.g.* (**214**)-(**217**).



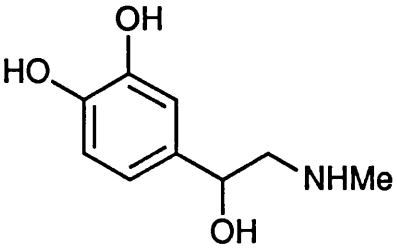
3,4-Dihydroxymandelic acid. (**213**)



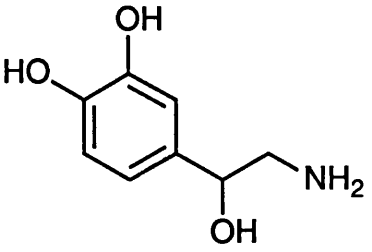
DOPA. (**214**)



Dopamine. (**215**)



Epinephrine. (**216**)



Normetanephrine. (**217**)

Figure 155

It also has a similar biological activity to dopamine (**215**), epinephrine (**216**) and normetanephrine (**217**) in promoting the effect of gibberellic acid on lettuce hypocotyl elongation[130].

The racemate of (**213**) is commercially available. However there is no reported asymmetric synthesis of the compound, although it has been resolved by chiral chromatography[131].

It was decided to attempt an asymmetric synthesis of (**213**) as an application of the use of dithiane dioxide as a chiral hydroxy carbonyl anion equivalent. The addition of Na-(**63**) to a suitably protected aldehyde followed by the hydrolysis protocol and final alcohol deprotection should give the target compound.

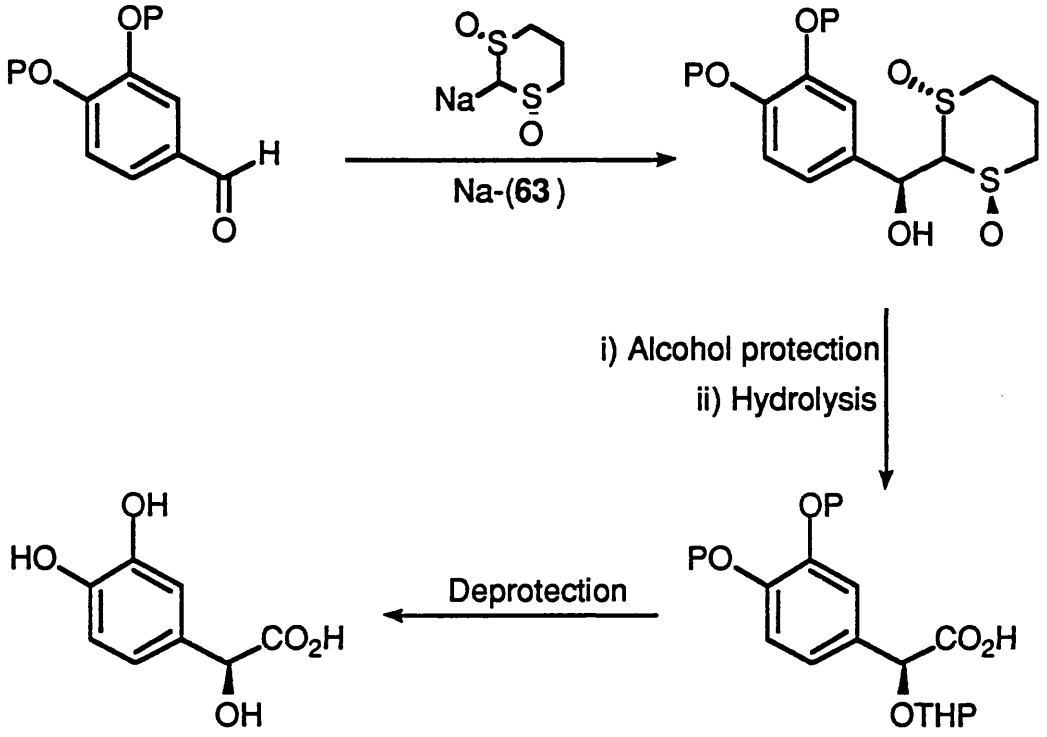


Figure 156

Due to the scarcity of homochiral dithiane dioxide at the time, it was decided initially to carry out the synthesis using racemic material in order to first optimise the reaction conditions.

So far, this racemic synthesis has been partially completed and this work is described briefly in the next section.

6.2 Synthesis.

Commercially available 3,4-dihydroxybenzaldehyde (**218**) was protected as the di-TBDMS ether (**219**), by treatment with TBDMS-Cl and imidazole in DMF[132].

Figure 157

The aldehyde (**219**) was then reacted with Na-(**63**) under the standard equilibrating conditions, at 0 °C in pyridine/THF.

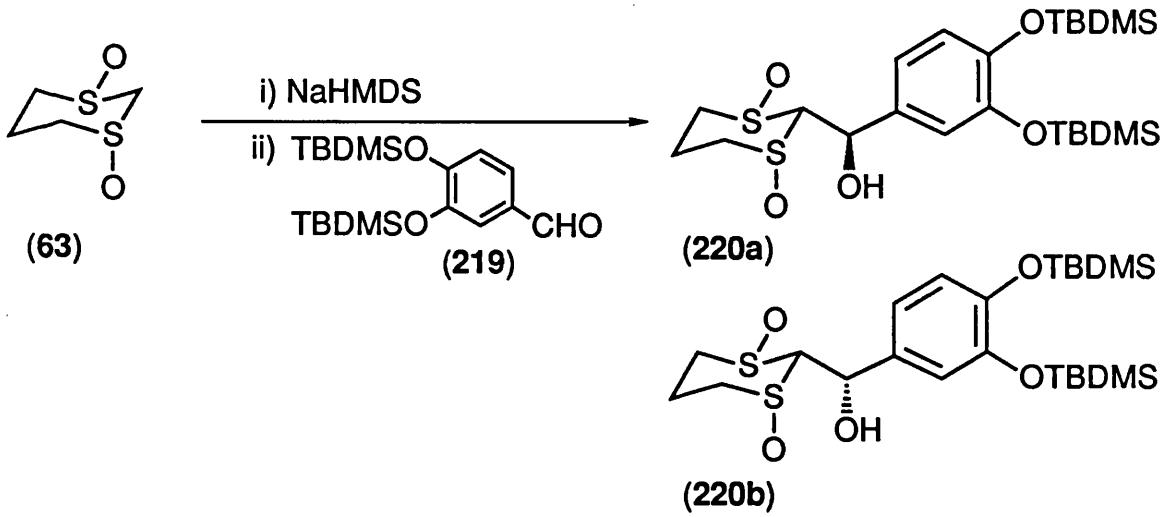


Figure 158

The adducts (**220a**) and (**220b**) were produced in a 96:4 ratio as determined by NMR analysis of the crude reaction mixture. This is very comparable with the selectivity observed with other aromatic aldehydes. The major isomer (**220a**) was isolated pure in 56% yield after column chromatography. The alcohol was then protected as the THP ether (**221**), by treatment with dihydropyran and catalytic tosic acid.

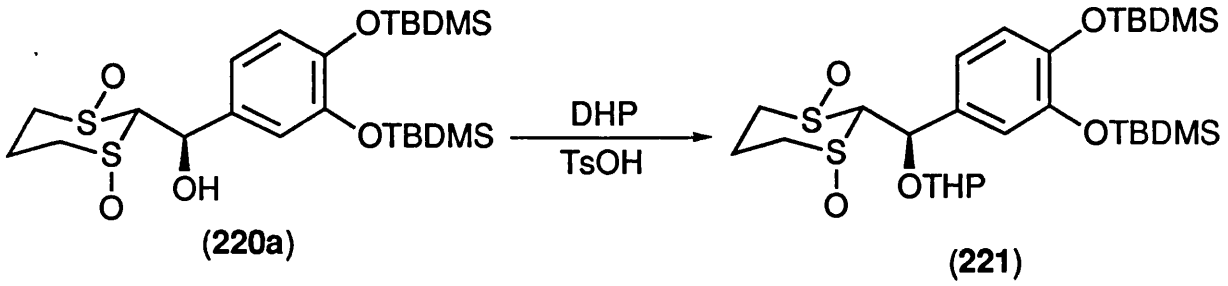
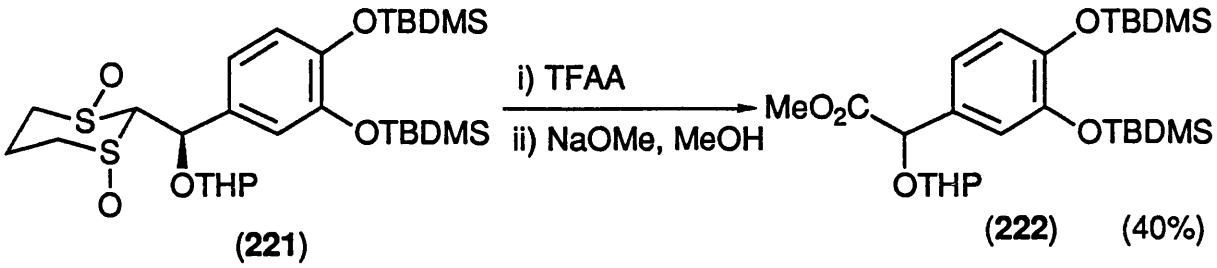


Figure 159

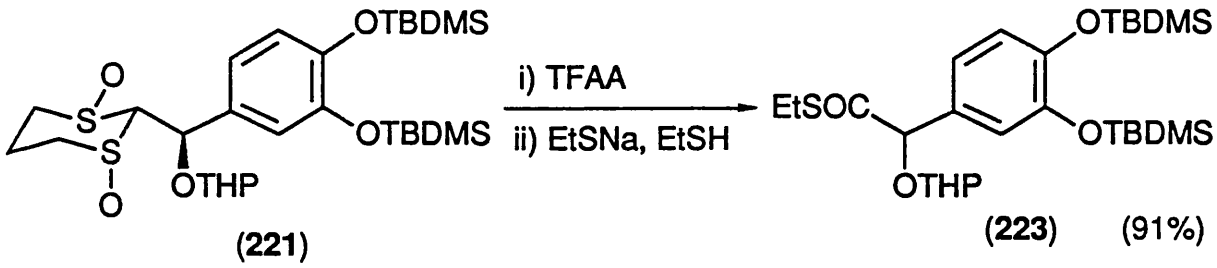
The dithiane dioxide moiety now had to be transformed to a carboxylic acid. The "one-pot" TFAA/sodium methoxide hydrolysis conditions were applied to (221).



(221) (222) (40%)

Figure 160

The methyl ester (222) was produced in moderate yield. However, since these conditions were subsequently shown to partially racemize the chiral centre of a similar compound (see Ch 5), this reaction is unlikely to be of use when attempting an asymmetric synthesis. The "one-pot" TFAA/ethanthiolate conditions were also applied to (221).



(221) (223) (91%)

Figure 161

This gave the ethane thiol (223) in excellent yield.

Unfortunately, due to insufficient time and material the synthesis has not been taken any further. Transformation of the ethanethiol to a carboxylic acid and deprotection of the alcohols would complete the synthesis in the racemic series. The ethanethiol to carboxylic acid reaction has been achieved on the unsubstituted mandelic acid (211), (Figure 152, chapter 5) and an acid hydrolysis should remove the TBDMS and THP protecting groups. It should therefore be possible to synthesise homochiral 3,4-dihydroxymandelic acid using this approach.

EXPERIMENTAL.

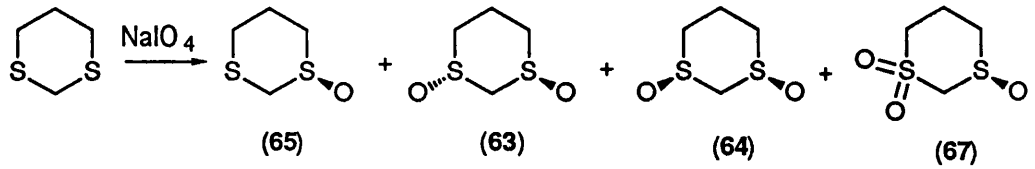
Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Proton and ^{13}C NMR spectra were recorded on a Jeol 270 MHz or a Bruker 250 MHz instrument. Infra-red spectra were measured on a Perkin-Elmer 1310 spectrophotometer.

THF was distilled from sodium immediately prior to use. Pyridine was distilled from potassium hydroxide and then stored over molecular sieves and under nitrogen until required. DMF was distilled from molecular sieves and then stored over more molecular sieves and under nitrogen until required. Dichloromethane was distilled from CaH and stored over molecular sieves and under nitrogen until required.

All anion and Pummerer reactions were performed in flame dried apparatus under a nitrogen atmosphere. All aldehydes and imines were recrystallized or distilled from $CaCl_2$ and stored under nitrogen until required. TFAA was distilled from $CaCl_2$ immediately prior to use.

All couping constants are given in Hertz.

Periodate oxidation of 1,3-dithiane



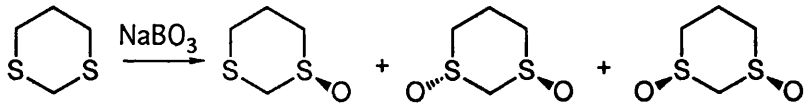
To a suspension of 1,3-dithiane (40g, 0.33mol) in methanol (1000ml) and water (100ml) was added sodium periodate (157g, 0.73mol).The mixture was stirred at room temperature for 48hrs. Dimethyl sulphide (12.2ml, 0.17mol) was added to the reaction mixture and the solvents evaporated, azeotroping with toluene (x3). The residue was placed on a short pad of silica gel and washed through with 30% methanol/acetone. The filtrate was evaporated to dryness. Chromatography on silica gel with 0-30% methanol/acetone as the eluant yielded, **1,3-dithiane-1-oxide** (**65**) (1.81g, 4%). An analytical sample was recrystallised from chloroform/cyclohexane, m.p. 86 °C (lit.[133], 87-88 °C); δ_H ($CDCl_3$) 4.02 (1H, dd, *J* 11.1 and 2.5, 2-H_{eq}), 3.66 (1H, d, *J* 11.1, 2-H_{ax}), 3.33 (1H, m, 6-H_{eq}), 2.73-2.46 (4H, m, 4-H_{ax}, 4-H_{eq}, 5-H_{eq} and 6-H_{ax}), 2.22 (1H, m, 5-H_{ax}).

***trans*-1,3-dithiane-1,3-dioxide** (**63**) (26.9g, 53%). An analytical sample was recrystallized from methanol, m.p. 170-171 °C; Rf (acetone) 0.2; (Found: C, 31.6; H, 5.3. Requires for $C_4H_8O_2S_2$: C, 31.7; H, 5.46%); υ_{max} (Nujol)/ cm^{-1} 1300, 1210 and 1040-1000s (S-O); δ (DMSO) 4.35 (2H, s, 2-H), 3.21 (2H, ddd, *J* 12.9, 6.4 and 5.9, 4-H_{eq} and 6-H_{ax}), 2.96 (2H, ddd, *J* 12.9, 6.0 and 5.1, 4-H_{ax} and 6-H_{eq}), 2.38, (2H, tt, *J* 6.4 and 5.3, 5-H); δ_C (DMSO) 61.6 (C-2), 47.5 (C-4 and C-6), 14.9 (C-5); m/z (EI) 152 (M^+, 20%), 103 (40), 90 (20), 73 (30), and 41 (100).

***cis*-1,3-dithiane-1,3-dioxide** (**64**) (5.1g, 10%). An analytical sample was recrystallized from absolute ethanol, m.p. 217 °C (lit[52]., 216 °C); Rf (acetone) 0.15; (Found: C, 31.3; H, 5.32. Requires for $C_4H_8O_2S_2$: C, 31.7; H, 5.4%); υ_{max} (Nujol)/ cm^{-1} 1050 (S-O), 1005 and 910; δ_H (DMSO) 4.55 (1H, dt, *J* 11.3 and 2.2, 2-H_{eq}), 4.17 (1H, d, *J* 11.3, 2-H_{ax}), 3.27 (2-H, dddd, *J* 12.7, 7.7, 2.4 and 2.2, 4-H_{eq} and 6-H_{eq}), 2.97 (2H, ddd, *J* 12.7, 10.5 and 2.7, 4-H_{ax} and 6-H), 2.59 (1H, ttd, *J* 16.6, 7.7 and 2.7, 5-H_{eq}), 1.63 (1H, ttd, *J* 16.2, 10.5 and 2.4, 5-H_{ax}); m/z (EI) 152 (M^+, 10%), 103 (40), 63 (20) and 41 (100).

1,3-dithiane-1,1,3-trioxide (67) (2.2g, 4%). An analytical sample was recrystallized from ethanol, m.p. 174 °C; Rf (acetone) 0.3; (Found: C, 28.4; H, 4.78. Requires for $C_4H_8O_3S_2$: C, 28.6; H, 4.79%); υ_{max} (Nujol)/ cm^{-1} 1310, 1300 (SO_2), 1120 (SO_2), 1040 (S-O), 1000 and 850; δ_H (DMSO) 4.92 (1H, dt, *J* 13.0 and 2.0, 2-H_{eq}), 4.58 (1H, dd, *J* 12.5 and 1.5, 2-H_{ax}), 3.30 (3H, m, 4-H_{eq}, 6-H_{eq} and 6-H_{ax}), 2.99 (1H, ddd, *J* 12.8, 10.3 and 2.6, 4-H_{ax}), 2.57 (1H, m, 5-H_{ax}); m/z (EI) 168 (M^+, 100%), 63 (90), 55 (75), 42 (45).

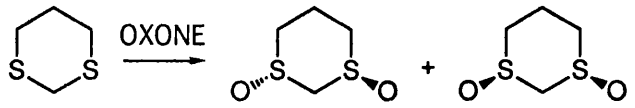
Perborate oxidation of 1,3-dithiane.



(65) (63) (64)

1,3-Dithiane (0.5g, 4.16mmol) was added to a solution of sodium perborate (1.41g, 9.15mmol) in glacial acetic acid (30ml). The mixture was stirred at 55 °C for 72 hrs. The reaction mixture was filtered and evaporated, azeotroping with toluene (x2).The ^1H NMR of the crude product indicated a mixture of (**65**), (**63**) and (**64**) in a 1 : 2.5 : 1.6 ratio. Flash chromatography on silica gel with acetone as the eluant afforded (**63**), 1.19g (30%) analysis as above.

Oxone oxidation of 1,3-dithiane.



(63) (64)

To a solution of 1,3-dithiane (2.0g, 16.63mmol) in acetone (160ml) was added a solution of Oxone (11.7g; 38.26mmol, 2.3 equiv. of oxidant) in water (160ml) at 0 °C. Stirring was continued at 0 °C for 15 mins. Dimethyl sulphide (0.52g, 8.32mmol) was added and stirring continued for a further 5 mins. The solvents were then evaporated, azeotroping with toluene (x2). The ^1H NMR of the crude product indicated a mixture of (**63**) and (**64**) in a 2 : 1 ratio. Flash chromatography on silica gel with acetone as the eluant afforded impure (**63**), 1.6g. Recrystallization from methanol gave a pure sample of (**63**), 0.35g (14%) analysis as above.

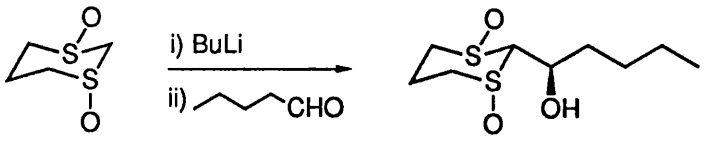
General method for monitoring M-HMDS reactions.

Dithiane dioxide (**63**) (0.05 g, 0.328 mmol) was dissolved in pyridine (2.5 ml) with warming and then diluted with THF (1.5 ml) before cooling to 0 °C, under nitrogen. To this was added a solution of the HMDS base (0.394 mmol). Stirring was continued at 0 °C for 0.5 hr. An excess of aldehyde (typically 0.5 mmol) was then added at the required reaction temperature and stirring continued. Samples (0.2 ml) were removed by syringe and quenched by addition to ethanol (1 ml) and aqueous HCl (2M, 0.1 ml, 0.2 mmol) at the reaction temperature. The solvents were then evaporated and the residue taken up in aqueous ammonia solution (2M, 1.5 ml). The solution was evaporated. The residue was dissolved in 50% ethanol/water (1 ml) and the solution either analysed by HPLC or filtered through a short pad of silica gel, eluting with acetone and analysed by NMR after evaporation of the acetone.

General method for monitoring BuLi reactions.

Dithiane dioxide (**63**) (0.05 g, 0.328 mmol) was dissolved in pyridine (2.5 ml) with warming and then diluted with THF (1.5 ml) before cooling to 0 °C, under nitrogen. A solution of BuLi (1.6M in hexanes) was then added dropwise until permanent appearance of a yellow-orange colour. An excess of aldehye (typically 0.5 mmol) was then added at the required reaction temperature and stirring continued. Samples were removed and treated as above before analysis.

1-(RS)-3-(RS)-α-(RS)-α-Butyl-1,3-dithiane-1,3-dioxide-2-methanol, (83a).

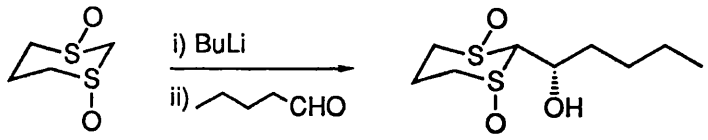


(63) (83a)

Dithiane dioxide (**63**) (0.05g, 0.329mmol) was dissolved in pyridine (2.5ml) with warming and then diluted with THF (1.5ml) before cooling to 0 °C, under nitrogen. To this was added dropwise a 1.6M solution of BuLi in hexane until a permanant yellow colour was achieved, (approx. 0.3ml, 0.48 mmol). An excess of valeraldehye (0.05ml, 0.48 mmol) was then added

in one portion. Stirring was continued for 10 mins at 0 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (10ml) and aqueous HCl (2M, 0.82ml, 1.64mmol) at 0 °C. The solvents were then evaporated. Chromatography on silica gel with 80% acetone/petrol as the eluant afforded (**83a**) (0.025g, 32%). An analytical sample was recrystallized from toluene, m.p. 150-152 °C; Rf (acetone) 0.25; (Found: C, 44.7; H, 7.70. Requires for $C_9H_{18}O_3S_2$: C, 45.1; H, 7.60%); υ_{max} (Nujol)/ cm^{-1} 3250 (O-H), 1020 (S-O); δ_H (DMSO) 5.40 (1H, d, *J* 6.6, OH), 4.26 (1H, m, C<u>H</u>OH), 3.83 (1H, d, *J* 4.4, 2-H), 3.51 (1H, m, 4-H), 3.00 (3H, m, 4-H and 2x 6-H), 2.60-2.15 (2H, m, 2x 5-H), 1.68 (2H, q, *J* 1.7, C<u>H</u>$_2$CHOH), 1.50-1.20 (4H, m, CH_2CH_2), 0.88 (3H, t, *J* 7.1, CH_3); m/z (EI) 238 (M^+, 100%), 122 (80), 103 (40), 85 (30), 73 (35).

<u>1-(RS)-3-(RS)-α-(SR)-α-Butyl-1,3-dithiane-1,3-dioxide-2-methanol.</u> <u>(83b).</u>

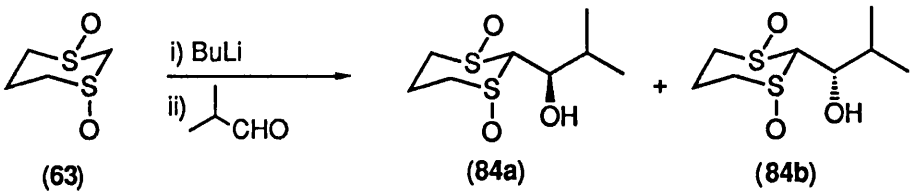


(63) (83b)

Dithiane dioxide (**63**) (0.05g, 0.329mmol) was dissolved in pyridine (2.5ml) with warming and then diluted with THF (1.5ml) before cooling to -78 °C, under nitrogen. To this was added dropwise a 1.6M solution of BuLi in hexane until a permanant yellow colour was achieved, (approx. 0.3ml, 0.48 mmol). Stirring was continued at -78 °C for 5min. An excess of valeraldehye (0.05ml, 0.48 mmol) was then added in one portion. Stirring was continued for 10 mins at -78 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (10ml) and aqueous HCl (2M, 0.82ml, 1.64mmol) at -78 C. The solvents were then evaporated. Chromatography on silica gel with 80% acetone/petrol as the eluant afforded (**83b**) (0.031g, 40%). An analytical sample was recrystallized from chlorobenzene, m.p. 111-112 °C; Rf (acetone) 0.35; (Found: C, 45.5; H, 7.70. Requires for $C_9H_{18}O_3S_2$: C, 45.4; H, 7.60%); υ_{max} (Nujol)/ cm^{-1} 3300 (O-H), 990 (S-O); δ_H (DMSO) 5.50 (1H, d, *J* 5.5, OH), 4.29 (1H, m, C<u>H</u>OH), 4.04 (1H, d, *J* 3.9, 2-H), 3.47 (1H, ddd, *J* 12.3, 6.2 and 4.0, 4-H), 3.06 (3H, m, 4-H and 2x 6-H), 2.50-2.20 (2H, m, 2x 5-H), 1.77 (2H, q, *J*

7.0, $C\underline{H}_2CHOH$), 1.52 (1H, m, $\underline{H}CHCH_2$), 1.30 (3H, m, $HC\underline{H}CH_2$), 0.88 (3H, t, *J* 7.1, $C\underline{H}_3$); m/z (EI) 238 (M^+, 100%), 172 (50), 122 (90), 73 (50).

1-(RS)-3-(RS)-α-(SR)-α-(1-Methylethyl)-1,3-dithiane-1,3-dioxide-2-methanol, (84a) and 1-(RS)-3-(RS)-α-(RS)-α-(1-Methylethyl)-1,3-dithiane-1,3-dioxide-2-methanol, (84b).



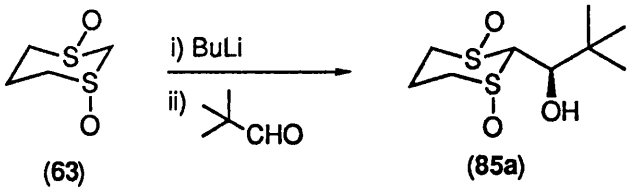
(63) (84a) (84b)

Dithiane dioxide (**63**) (0.05g, 0.329mmol) was dissolved in pyridine (2.5ml) with warming and then diluted with THF (1.5ml) before cooling to -78 °C, under nitrogen. To this was added dropwise a 1.6M solution of BuLi in hexane until a permanant yellow colour was achieved, (0.3ml, 0.48 mmol). Stirring was continued at -78 °C for 5min. An excess of isobutyraldehye (0.05ml, 0.55 mmol) was then added in one portion. Stirring was continued for 2 mins at -78 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (10ml) and aqueous HCl (2M, 0.82ml, 1.64mmol) at -78 °C. The solvents were then evaporated. Chromatography on silica gel with 80% acetone/petrol as the eluant afforded (**84a**) (0.026g, 35%). An analytical sample was recrystallized from toluene, m.p. 135 °C; Rf (acetone) 0.35; (Found: C, 42.9; H, 7.40. Requires for $C_8H_{16}O_3S_2$: C, 42.8; H, 7.20%); υ_{max} (Nujol)/ cm^{-1} 3250 (O-H), 1000 (S-O); δ_H (DMSO) 5.39 (1H, d, *J* 5.3, OH), 4.20 (1H, d, *J* 3.7, 2-H), 4.07 (1H, ddd, *J* 6.7, 5.2 and 3.7, $C\underline{H}OH$), 3.49 (1H, ddd, *J* 12.7, 6.7 and 4.5, 4-H), 3.20-3.00 (3H, m, 4-H and 2x 6-H), 2.37 (2H, m, 2x 5-H), 2.03 (1H, octet, *J* 6.7, $C\underline{H}Me_2$), 0.96 (3H, d, *J* 6.8, CH_3), 0.93 (3H, d, *J* 6.8, CH_3); m/z (EI) 224 (M^+, 7%), 123 (20), 119 (25).

Continued elution of the column gave (**84b**) (0.026g, 35%). An analytical sample was recrystallized from chlorobenzene, m.p. 177-178 °C; Rf (acetone) 0.25; (Found: C, 42.9; H, 7.40. Requires for $C_8H_{16}O_3S_2$: C, 42.8; H, 7.20%); υ_{max} (Nujol)/ cm^{-1} 3230 (O-H), 1010 (S-O); δ_H (DMSO) 5.44 (1H, d, *J* 6.8, OH), 3.97 (2H, m, $C\underline{H}OH$ and 2-H), 3.50 (1H, ddd, *J*

12.0, 5.2 and 2.2, 4-H), 3.15-3.00 (3H, m, 4-H and 2x 6-H), 2.53 (1H, m, 5-H), 2.22 (1H, m, 5-H), 2.04 (1H, octet, *J* 6.6, C<u>H</u>Me$_2$), 0.95 (3H, d, *J* 6.6, CH$_3$), 0.88 (3H, d, *J* 6.6, CH$_3$); m/z (EI) 224 (M$^+$, 3%), 181 (10), 123 (25).

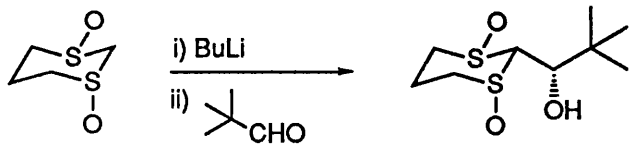
<u>1-(RS)-3-(RS)-α-(RS)-α-(1,1-Dimethylethyl)-1,3-dithiane-1,3-dioxide-2-methanol, (85a).</u>



(63) (85a)

Dithiane dioxide (**63**) (0.05g, 0.329mmol) was dissolved in pyridine (2.5ml) with warming and then diluted with THF (1.5ml) before cooling to 0 °C, under nitrogen. To this was added dropwise a 1.6M solution of BuLi in hexane until a permanant yellow colour was achieved, (0.3ml, 0.48 mmol). An excess of pivalaldehye (0.05ml, 0.46 mmol) was then added in one portion. Stirring was continued for 60 mins at 0 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (10ml) and aqueous HCl (2M, 0.82ml, 1.64mmol) at 0 °C. The solvents were then evaporated. Chromatography on silica gel with 80% acetone/petrol as the eluant afforded (**85a**) (0.053g, 68%). An analytical sample was recrystallized from CCl_4/EtOAc, m.p. 188-190 °C; Rf (acetone) 0.30; (Found: C, 45.4; H, 7.90. Requires for $C_9H_{18}O_3S_2$: C, 45.4; H, 7.50%); υ_{max} (Nujol)/ cm^{-1} 3250 (O-H), 1020 (S-O); δ_H (DMSO) 5.76 (1H, d, *J* 6.2, OH), 4.02 (1H, d, *J* 6.2, C<u>H</u>OH), 3.95 (1H, s, 2-H), 3.57 (1H, dm, *J* 13.0, 4-H), 3.18 (1H, ddd, *J* 13.0, 13.0 and 3,0, 4-H), 3.05 (1H, ddd, *J* 14.0, 14.0 and 2.5, 6-H), 2.91 (1H, dm, *J* 14.0, 6-H), 2.60 (1H, m, 5-H), 2.22 (1H, dm, *J* 5-H), 0.89 (9H, s, C(C<u>H</u>$_3$)$_3$); δ_C (DMSO) 75.8 (C-2), 71.2 (COH), 52.6 (C-4 or C-6), 44.9 (C-4 or C-6), 35.7 (<u>C</u>(CH$_3$)$_3$), 26.0 (C(<u>C</u>H$_3$)$_3$), 15.5 (C-5); m/z (CI) 239 ((M+1)$^+$, 50%), 153 (60), 92 (100), 87 (60).

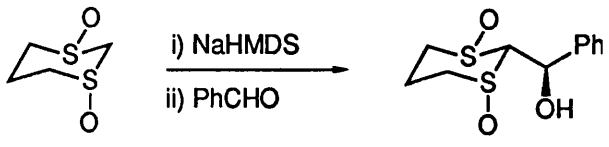
<u>1-(RS)-3-(RS)-α-(SR)-α-(1,1-Dimethylethyl)-1,3-dithiane-1,3-dioxide-2-methanol, (85b).</u>



(63) (85b)

Dithiane dioxide (**63**) (0.05g, 0.329mmol) was dissolved in pyridine (2.5ml) with warming and then diluted with THF (1.5ml) before cooling to -78 °C, under nitrogen. To this was added dropwise a 1.6M solution of BuLi in hexane until a permanant yellow colour was achieved, (0.3ml, 0.48mmol). Stirring was continued at -78 °C for 5min. An excess of pivalaldehye (0.05ml, 0.46 mmol) was then added in one portion. Stirring was continued for 40 mins at -78 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (10ml) and aqueous HCl (2M, 0.82ml, 1.64mmol) at -78 °C. The solvents were then evaporated. Chromatography on silica gel with 80% acetone/petrol as the eluant afforded (**85b**) (0.022g, 28%). An analytical sample was recrystallized from toluene, m.p. 157-160 °C; Rf (acetone) 0.35; (Found: C, 45.4; H, 7.90. Requires for $C_9H_{18}O_3S_2$: C, 45.4; H, 7.60%); υ_{max} (Nujol)/ cm^{-1} 3200 (O-H), 1020 (S-O); δ_H ($CDCl_3$) 4.28 (1H, d, *J* 2.0, C<u>H</u>OH), 3.96 (1H, br.s, 2-H), 3.52 (1H, ddd, *J* 14.1, 11.4 and 4.9, 6-H), 3.37 (1H, ddd, *J* 13.4, 7.9 and 4.6, 4-H), 3.25 (1H, ddd, *J* 13.2, 8.3 and 4.4, 4-H), 3.08 (1H, ddd, *J* 14.1, 4.0 and 4.0, 6-H), 2.67 (1H, m, 5-H), 2.42 (1H, m, 5-H), 1.07 (9H, s, $C(C\underline{H}_3)_3$); δ_C (DMSO) 75.2 (C-2), 73.7 (COH), 50.3 (C-4 or C-6), 48.7 (C-4 or C-6), 40.3 ($\underline{C}(CH_3)_3$), 30.0 ($C(\underline{C}H_3)_3$), 19.1 (C-5); m/z (EI) 238 (M^+, 100%), 181 (40), 122 (40).

<u>1-(RS)-3-(RS)-α-(RS)-α-Phenyl-1,3-dithiane-1,3-dioxide-2-methanol, (86a).</u>

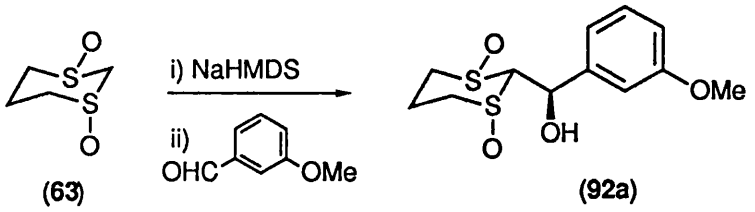


(63) (86a)

Dithiane dioxide (**63**) (0.1g, 0.657mmol) was dissolved in pyridine (5ml) with warming and then diluted with THF (3ml) before cooling to 0 °C, under nitrogen. To this was added a 1.0M solution of NaHMDS in THF (0.99ml, 0.99mmol). Stirring was continued at 0 °C for 0.5hr. An excess of benzaldehye (0.1ml, 0.98 mmol) was then added in one portion. Stirring was continued for 0.5hr at 0 °C. The reaction mixture was then transferred by syringe into a

rapidly stirred mixture of ethanol (15ml) and aqueous HCl (2M, 1.6ml, 3.2mmol) at 0 °C. The solvents were then evaporated under vacuum and the resulting white solid recrystallized from ethanol to give (**86a**) (0.13g, 77%). The mother liquor was evaporated to dryness. Chromatography on silica gel with acetone as the eluant afforded more (**86a**) (0.017g, 10%). Total yield of (**86a**) (0.147g, 87%), m.p. 187-188 °C; Rf (acetone) 0.25; (Found: C, 51.0; H, 5.50. Requires for $C_{11}H_{14}O_3S_2$: C, 51.1; H, 5.46%); υ_{max} (Nujol)/ cm^{-1} 3200 (OH), 1045 and 1010 (S-O); δ_H (DMSO) 7.5-7.25 (5H, m, Ph), 6.07 (1H, d, *J* 4.3, OH), 5.49 (1H, br. t, *J* 4.4, C<u>H</u>OH), 4.16 (1H, d, *J* 4.3, 2-H), 3.53 (1H, ddd, *J* 12.0, 4.8 and 1.5, 4-H_{eq}), 3.09 (1H, ddd, *J* 12.0, 12.0 and 2.3, 4-H_{ax}), 3.0-2.6 (2H, m, 2x 6-H), 2.55(1H, m, 5-H), 2.22 (1H, m, 5-H); δ_C (DMSO) 141.5 (Ar), 128.4 (2x Ar), 127.7 (Ar), 126.7(2x Ar), 79.0 (C-2), 67.8 (COH), 51.5 (C-4 or C-6), 45.9 (C-4 or C-6), 15.3 (C-5); m/z (CI) 259 (M+1, 10%), 153 (50), 107 (100).

<u>1-(RS)-3-(RS)-α-(RS)-α-(3-Methoxyphenyl)-1,3-dithiane-1,3-dioxide-2-methanol, (92a).</u>

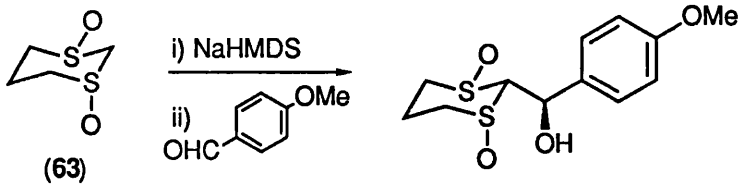


(63) (92a)

Dithiane dioxide (**63**) (0.075g, 0.49mmol) was dissolved in pyridine (3.75ml) with warming and then diluted with THF (2.25ml) before cooling to 0 °C, under nitrogen. To this was added a 1.0M solution of NaHMDS in THF (0.75ml, 0.75mmol). Stirring was continued at 0 °C for 0.5hr. An excess of *m*-anisaldehye (0.075ml, 0.61 mmol) was then added in one portion. Stirring was continued for 2.5hr at 0 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (10ml) and aqueous HCl (2M, 1.2ml, 2.4mmol) at 0 °C. The solvents were then evaporated under vacuum. Chromatography on silica gel with acetone as the eluant afforded (**92a**). The chromatographed material was recrystallized from ethanol (2 crops) to give colourless needles (0.091g, 64%), m.p. 202-203 °C; Rf (acetone) 0.24; (Found: C, 49.7; H, 5.62. Requires for $C_{12}H_{16}O_4S_2$: C, 50.0; H, 5.59%); υ_{max} (Nujol)/

cm^{-1} 3200 (OH), 1010 (S-O); δ_H (DMSO) 7.56 (1H, m, Ar), 7.28 (2H, m, Ar), 7.11 (1H, m, Ar), 6.32 (1H, d, *J* 5.0, OH), 5.71 (1H, dd, *J* 5.0 and 3.3, CHOH), 4.42 (1H, d, *J* 3.3, 2-H), 4.02 (3H, s, OMe), 3.78 (1H, dm, *J* 12.1, 4-H_{eq}), 3.36 (1H, dt, *J* 11.2 and 2.3, 4-h_{ax}), 3.19-3.03 (2H, m, 2x 6-H), 2.55 (1H, m, 5-H), 2.22 (1H, m, 5-H); δ_C (DMSO) 159.1 (Ar), 143.0 (Ar), 118.5 (Ar), 112.7 (Ar), 112.0 (Ar), 78.7 (C-2), 67.5 (COH), 54.9 (OMe), 50.9 (C-4 or C-6), 15.0 (C-5); m/z (EI) 288 (M^+, 15%), 222 (15), 152 (30), 136 (100), 103 (40).

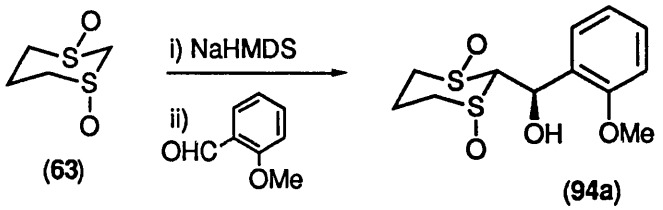
1-(RS)-3-(RS)-α-(RS)-α-(4-Methoxyphenyl)-1,3-dithiane-1,3-dioxide-2-methanol. (93a).



(63) (93a)

Dithiane dioxide (**63**) (0.075g, 0.49mmol) was dissolved in pyridine (3.75ml) with warming and then diluted with THF (2.25ml) before cooling to 0 °C, under nitrogen. to this was added a 1.0M solution of NaHMDS in THF (0.75ml, 0.75mmol). Stirring was continued at 0 °C for 0.5hr. An excess of *p*-anisaldehye (0.075ml, 0.61 mmol) was then added in one portion. Stirring was continued for 2.5hr at 0 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (10ml) and aqueous HCl (2M, 1.2ml, 2.4mmol) at 0 °C. The solvents were then evaporated under vacuum. Chromatography on silica gel with acetone as the eluant afforded (**93a**). The chromatographed material was recrystallized from ethanol (2 crops) to give colourless needles. (0.072g, 72%).m.p. 158 °C; Rf (acetone) 0.21; (Found: C, 50.1; H, 5.67. Requires for $C_{12}H_{16}O_4S_2$: C, 50.0; H, 5.59%); υ_{max} (Nujol)/ cm^{-1} 3200 (OH), 1005 (S-O); δ_H (DMSO) 7.62 (2H, d, *J* 8.7, Ar), 7.20 (2H, d, *J* 8.7, Ar), 6.22 (1H, d, *J* 4.8, OH), 5.69 (1H, dd, *J* 4.8 and 3.5, CHOH), 4.35 (1H, d, *J* 3.5, 2-H), 4.01 (3H, s, OMe), 3.77 (1H, dm, *J* 11.7, 4-H_{eq}), 3.33 (1H, dt, *J* 12.4 and 2.3, 4-H_{ax}), 3.22-3.01 (2H, m, 2x 6-H), 2.82 (1H, dm, *J* 15.0, 5-H), 2.46 (1H; dm, *J* 15.0, 5-H); δ_C (DMSO) 158.7 (Ar), 133.2 (Ar), 127.7 (2x Ar), 113.6 (2x Ar), 78.9 (C-2), 67.4 (COH), 55.1 (OMe), 50.8 (C-4 or C-6), 45.7 (C-4 or C-6), 15.0 (C-5); m/z (CI) 271 (M-H_2O, 100%), 255 (80), 238 (70).

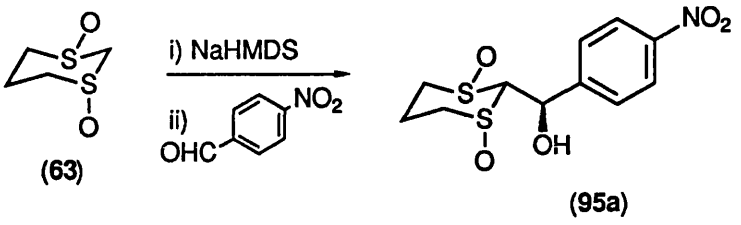
1-(RS)-3-(RS)-α-(RS)-α-(2-Methoxyphenyl)-1,3-dithiane-1,3-dioxide-2-methanol, (94a).



(63) (94a)

Dithiane dioxide (**63**) (0.15g, 0.49mmol) was dissolved in pyridine (7.5ml) with warming and then diluted with THF (4.5ml) before cooling to 0 °C, under nitrogen. to this was added a 1.0M solution of NaHMDS in THF (1.2ml, 1.20mmol). Stirring was continued at 0 °C for 0.5hr. *o*-Anisaldehye was then added (0.16g, 1.20mmol), as a solution in THF. Stirring was continued for 7.5hr at 0 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (20ml) and aqueous HCl (2M, 2.5ml, 4.93mmol) at 0 °C. The solvents were then evaporated under vacuum and the residue taken up in aqueous ammonia solution (2M, 20ml). The solution was evaporated to dryness. Chromatography on silica gel with 70-100% acetone/petrol as the eluant afforded (**94a**) (0.216g, 76%). An analytical sample was recrystallized from ethanol, m.p. 167 °C; Rf (acetone) 0.16; (Found: C, 49.9; H, 5.82. Requires for $C_{12}H_{16}O_4S_2$: C, 50.0; H, 5.59%); υ_{max} (Nujol)/ cm^{-1} 3230 (OH), 1010 (S-O); δ_H (DMSO) 7.67 (1H, dd, *J* 7.5 and 1.8, Ar), 7.30 (1H, ddd, *J* 7.5, 7.5 and 1.8, Ar), 7.02 (2H, m, Ar), 5.80 (1H, d, *J* 5.8, OH), 5.76 (1H, dd, *J* 5.8 and 3.5, CHOH), 3.86 (1H, d, *J* 3.5, 2-H), 3.78 (3H, s, OMe), 3.51 (1H, ddd, *J* 12.4, 5.1 and 2.2, 4-H_{eq}), 3.09 (1H, ddd, *J* 12.4, 12.4 and 2.3, 4-H_{ax}), 2.89 (2H, m, 2x 6-H), 2.51 (1H, m, 5-H), 2.18 (1H, dm, *J* 15.0, 5-H); δ_C (DMSO) 155.2 (Ar), 128.9 (Ar), 128.7 (Ar), 128.1 (Ar), 120.2 (Ar), 110.7 (Ar), 77.1 (C-2), 63.0 (COH), 55.6 (OMe), 50.9 (C-4 or C-6), 45.8 (C-4 or C-6), 15.1 (C-5); m/z (EI) 288 (M^+, 100%), 222 (35), 206 (45), 136 (60), 119 (70).

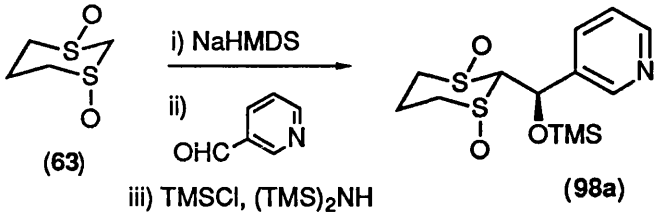
1-(RS)-3-(RS)-α-(RS)-α-(4-Nitrophenyl)-1,3-dithiane-1,3-dioxide-2-methanol, (95a).



(63) (95a)

Dithiane dioxide (**63**) (0.15g, 0.99mmol) was dissolved in pyridine (7.5ml) with warming and then diluted with THF (4.5ml) before cooling to 0 °C, under nitrogen. to this was added a 1.0M solution of NaHMDS in THF (1.18ml, 1.18mmol). Stirring was continued at 0 °C for 0.5hr. *p*-Nitrobenzaldehye was then added (0.18g, 1.18mmol), as a solution in THF (1ml). Stirring was continued for 5hrs at 0 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (20ml) and aqueous HCl (2M, 2.5ml, 4.93mmol) at 0 °C. The solvents were then evaporated under vacuum.and the residue taken up in aqueous ammonia solution (2M, 20ml). The solution was evaporated to dryness. Chromatography on silica gel with acetone as the eluant afforded (**95a**) (0.127g, 42%). An analytical sample was recrystallized from ethanol, m.p. 227-230 °C; Rf (50% acetone/ethanol) 0.55; (Found: C, 43.4; H, 4.35; N, 4.55. Requires for $C_{11}H_{13}NO_5S_2$: C, 43.6; H, 4.32; N, 4.62%); υ_{max} (Nujol)/ cm^{-1} 3250 (OH), 1020 (S-O); δ_H (DMSO) 8.26 (2H, d, *J* 8.7, Ar), 7.75 (2H, d, *J* 8.7, Ar), 6.49 (1H, d, *J* 5.1, OH), 5.60 (1H, dd, *J* 5.1 and 3.6, CHOH), 4.32 (1H, d, *J* 3.7, 2-H), 3.57 (1H, ddm, *J* 11.7 and 3.0, 4-H_{eq}), 3.10 (1H, dt, *J* 12.2 and 2.3, 4-H_{ax}), 3.00-2.78 (2H, m, 2x 6-H), 2.60 (1H, dm, *J* 15.0, 5-H), 2.24 (1H, dm, *J* 15.0, 5-H); δ_C (DMSO) 147.0 (Ar), 128.1 (2x Ar), 123.5 (2x Ar), 78.5 (C-2), 67.6 (COH), 51.4 (C-4 or C-6), 46.0 (C-4 or C-6), 15.3 (C-5); m/z (CI) (M+1, 2%), 153 (100), 122 (40).

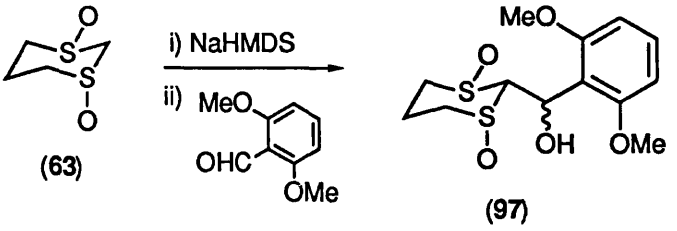
1-(RS)-3-(RS)-α-(RS)-α-(3-Pyridyl)-1,3-dithiane-1,3-dioxide-2-trimethylsilyloxymethane, (98a).



(63) (98a)

Dithiane dioxide (**63**) (0.10g, 0.657mmol) was dissolved in pyridine (5ml) with warming and then diluted with THF (3ml) before cooling to 0 °C, under nitrogen. To this was added a 1.0M solution of NaHMDS in THF (0.8ml, 0.8mmol). Stirring was continued at 0 °C for 0.5hr. An excess of 3-Pyridinecarboxaldehye was then added (0.1 ml, 1.06 mmol). Stirring was continued for 0.5hr at 0 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (15ml) and aqueous HCl (2M, 1.6ml, 3.2mmol) at 0 °C. The solvents were then evaporated under vacuum. The mixture was suspended in pyridine (5ml) at room temperature in a dried flask, under nitrogen. To this was added chlorotrimethylsilane (0.29ml,2.30mmol) and 1,1,1,3,3,3-hexamethyldisilazane (0.41ml, 3.61mmol). Stirring was continued at room temperature for 1.5 hrs. The reaction mixture was poured into water (50ml) and extracted with CH_2Cl_2 (50ml x2). Combined organics were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with acetone as the eluant afforded (**98a**) (0.121g, 56%) and a mixture of (**98a**) and (**98b**) (0.37g, 17%). An analytical sample of (**98a**) was recrystallized from EtOAc, m.p. 170-171 °C; Rf (acetone) 0.18; (Found: C, 47.3; H, 6.47; N, 4.23. Requires for $C_{13}H_{21}NO_3S_2Si$: C, 47.1; H, 6.38; N, 4.25%); υ_{max} (Nujol)/ cm^{-1} 1025 (S-O); δ_H ($CDCl_3$) 8.64 (1H, br. s, Ar), 8.56 (1H, d, *J* 4.8, Ar), 7.87 (1H, *J* 7.9, Ar), 7.33 (1H, dd, *J* 7.9 and 4.8, Ar), 5.70 (1H, d, *J* 4.4, CHOH), 3.67 (1H, dd, *J* 10 and 6.0, 4-H), 3.32 (1H, d, *J* 4.4, 2-H), 3.11 (1H, dt, *J* 14.0 and 3.5, 4-H), 2.88 (2H, m, 2x 6-H), 2.58 (1H, m, 5-H), 2.35 (1H, m, 5-H), 0,13 (9H, s, 3xCH_3, TMS); δ_C ($CDCl_3$) 149.8 (Ar), 148.1 (Ar), 135.9 (Ar), 134.6 (Ar), 123.5 (Ar), 82.0 (C-2), 67.9 (COH), 51.6 (C-4 or C-6), 46.2 (C-4 or C-6), 14.5 (C-5) -0.16 (3x CH_3, TMS); m/z (CI) 332 (M+1, 40%), 331 (60), 314 (60), 283 (100), 193 (70), 177 (60), 73 (80).

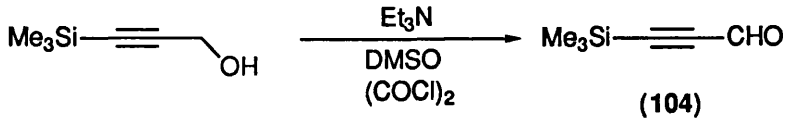
1-(RS)-3-(RS)-α-(RS/SR)-α-(2,6-Dimethoxyphenyl)-1,3-dithiane-1,3-dioxide-2-methanol, (97).



(63) (97)

Dithiane dioxide (**63**) (0.1g, 0.657mmol) was dissolved in pyridine (5ml) with warming and then diluted with THF (3ml) before cooling to 0 °C, under nitrogen. To this was added a 1.0M solution of NaHMDS in THF (0.8ml, 0.8mmol). Stirring was continued at 0 °C for 0.5hr. 2,6-Dimethoxybenzaldehyde (0.13g, 0.8mmol) was then added as a solution in THF (1ml). Stirring was continued for 1 hr at 0 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (16ml) and aqueous HCl (2M, 1.6ml, 3.29mmol) at 0 °C. The solvents were then evaporated under vacuum. Chromatography on silica gel with acetone as the eluant afforded (**97**) (0.139g, 66%), as a 1:1.3 ratio of diastereomers. An analytical sample was recrystallized from acetone/petrol, m.p. 142-145 °C; Rf (acetone) 0.33; (Found: C, 48.8; H, 5.76. Requires for $C_{13}H_{18}O_5S_2$: C, 49.0; H, 5.70%); υ_{max} (Nujol)/ cm^{-1} 3530 (OH), 1040 (S-O); δ_H[136] (DMSO) 7.29[b] (1H, t, *J* 8.5, *o*-Ar), 7.26[a] (1H, t, *J* 8.5, *o*-Ar), 6.68[b] (2H, d, *J* 8.5, *m*-Ar), 6.67[a] (2H, d, *J* 8.5, *m*-Ar), 5.99[b] (1H, dd, *J* 8.1 and 5.7, C<u>H</u>OH), 5.85[a] (1H, dd, *J* 9.4 and 7.0, C<u>H</u>OH), 5.12[a] (1H, d, *J* 9.4, OH), 4.81[b] (1H, d, *J* 5.7, OH), 4.44[b] (1H, d, *J* 8.1, 2-H). 4.08[a] (1H, d, *J* 7.0, 2-H), 3.79[a] (3H, s, O<u>CH</u>$_3$), 3.78[b] (3H, s, O<u>CH</u>$_3$), 3.52 (1H, m, 4-H), 3.40-2.95 (3H, m, 4-H and 2x 6-H), 2.52-2.12 (2H, m, 2x 5-H); δ_C[136] (DMSO) 158.9[b] (2x COMe), 158.7[a] (2x COMe), 130.8[a] (Ar), 130.3[b] (Ar), 116.1[a] (Ar), 115.6[b] (Ar), 105.22[a] (Ar), 105.17[b] (Ar), 77.4[b] (C-2), 75.9[a] (C-2), 64.2[b] (COH), 62.4[a] (COH), 56.5 (2x OCH_3), 49.4[a] (C-4 or C-6), 49.2[b] (C-4 or C-6), 45.7[a] (C-4 or C-6), 44.7[b] (C-4 or C-6), 15.1[a] (C-5), 14.7[b] (C-5); m/z (EI) 318 (M^+, 10%), 180 (30), 167 (100), 151 (50), 107 (40), 41 (35).

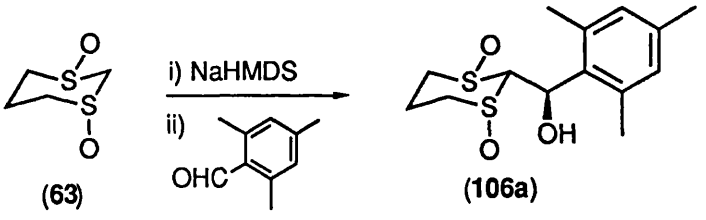
3-Trimethylsilyl-2-propyn-1-al, (104).



(104)

To a solution of oxalyl chloride (1.09g, 8.58mmol) in dry CH_2Cl_2, at -78 °C, was added a solution of DMSO (1.52g, 19.5mmol) in CH_2Cl_2 (5ml). Stiring was continued at -78 °C for 10 minutes. A solution of 3-trimethylsilyl-2-propyn-1-ol (1.0g, 7.80mmol) in CH_2Cl_2 (10ml) was then added dropwise and stirring continued at -78 °C for a further 15 minutes. The reaction mixture was allowed to warm to room temrerature and then poured into water (40ml) and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed sequentially with 2M HCl (x2), water, saturated $NaHCO_3$ and water and then dried ($MgSO_4$) and evaporated. The crude product was distilled from $CaCl_2$, to give a pale yellow oil, (**104**) (0.78g, 72%) b.p. 60 °C (20 mmHg) (lit.,[142] 52 °C (17 mmHg)); Rf (20% EtOAc/petrol) 0.87; δ_H ($CDCl_3$) 9.16 (1H, s, CHO), 0.26 (9H, s, $(CH_3)_3Si$).

1-(RS)-3-(RS)-α-(RS)-α-(2,4,6-Trimethylphenyl)-1,3-dithiane-1,3-dioxide-2-methanol, (106a).

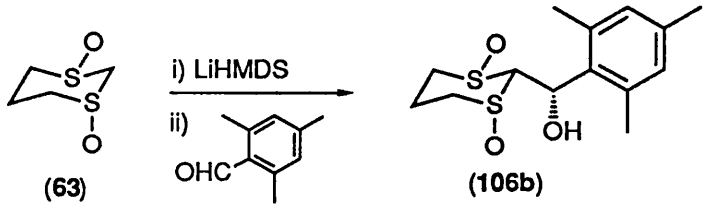


(63) (106a)

Dithiane dioxide (**63**) (0.25g, 1.64mmol) was dissolved in pyridine (12.5ml) with warming and then diluted with THF (7.5ml) before cooling to 0 °C, under nitrogen. To this was added a 1.0M solution of NaHMDS in THF (1.97ml, 1.97mmol). Stirring was continued at 0 °C for 0.5hr. Mesitaldehyde (0.36ml, 2.46mmol) was then added in one portion. Stirring was continued for 0.5hr at 0 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (40ml) and aqueous HCl (2M, 4.1ml, 8.2mmol) at 0 °C. The solvents were then evaporated under vacuum. The residue was portioned between water and CH_2Cl_2 and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (x2).

Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 25-50% acetone/EtOAc as the eluant afforded (**106a**) (0.108g, 22%). An analytical sample was recrystallized from $CH_2Cl_2/^iPr_2O$, m.p. 172 °C; Rf (acetone) 0.37; υ_{max} (Nujol)/ cm^{-1} 3220 (OH), 1000 (S-O); δ_H (DMSO) 6.76 (2H, s, Ar), 6.00 (1H, d, *J* 5.1, OH), 5.72 (1H, dd, *J* 7.3 and 5.1, C<u>H</u>OH), 4.02 (1H, d, *J* 7.3, 2-H), 3.37 (1H, m, 4-H), 3.06-2.92 (3H, m, 4-H and 2x 6-H), 2.55-2.25 (8H, m, 2x 5-H and 2x C<u>H</u>$_3$), 2.13 (3H, s, C<u>H</u>$_3$); δ_C (DMSO) 136.5 (Ar), 136.0 (2x Ar), 134.3 (Ar), 129.6 (2x Ar), 77.1 (C-2), 65.5 (COH), 50.3 (C-4 or C-6), 44.3 (C-4 or C-6), 20.8 (2x CH_3), 20.4 (CH_3), 14.4 (C-5); m/z (CI) 283 ((M-H_2O)+1, 1%), 153 (70), 149 (100).

<u>1-(RS)-3-(RS)-α-(SR)-α-(2,4,6-Trimethylphenyl)-1,3-dithiane-1,3-dioxide-2-methanol, (106b).</u>

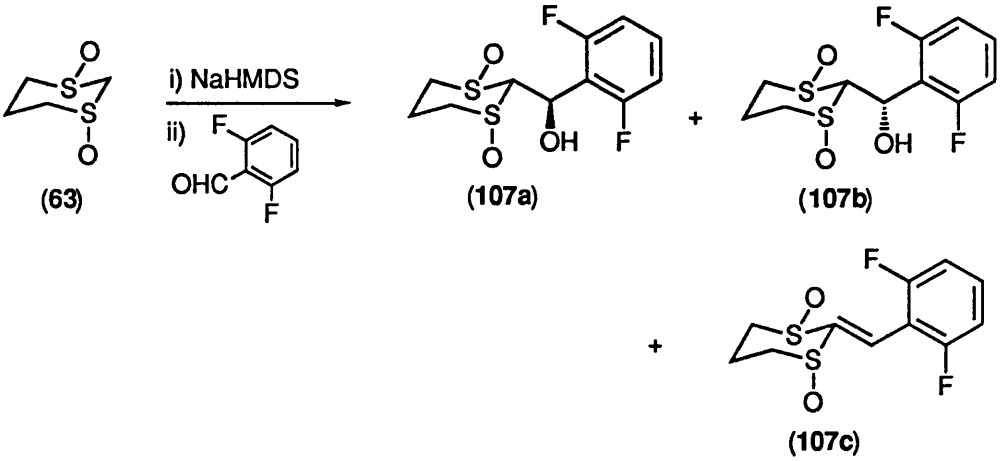


(63) (106b)

Dithiane dioxide (**63**) (0.4g, 2.63mmol) was dissolved in pyridine (20ml) with warming and then diluted with THF (12ml) before cooling to 0 °C, under nitrogen. To this was added a 1.0M solution of LiHMDS in THF (3.15ml, 3.15mmol). Stirring was continued at 0 °C for 0.5hr. The mixture was cooled to -78 °C. Mesitaldehye (0.46ml, 3.15mmol) was then added in one portion. Stirring was continued for 0.5hr at -78 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (66ml) and aqueous HCl (2M, 6.6ml, 13.1mmol) at -78 °C. The solvents were then evaporated under vacuum. Chromatography on silica gel with 25-50% acetone/EtOAc as the eluant afforded (**106b**) (0.068g, 9%). An analytical sample was recrystallized from EtOAc, m.p. 167 °C; Rf (acetone) 0.54; (Found: C, 55.33; H, 6.69. Requires for $C_{14}H_{20}O_3S_2$: C, 56.0; H, 6.71%); υ_{max} (Nujol)/ cm^{-1} (S-O); δ_H (DMSO) 6.75 (2H, s, Ar), 5.80 (1H, dd, *J* 8.0 and 3.6, C<u>H</u>OH), 5.37 (1H, d, *J* 3.6, OH), 4.35 (1H, d, *J* 8.0, 2-H), 3.47 (1H, m, 4-H), 3.18 (1H, m, 4-H), 3.01 (2H, m, 2x 6-H), 2.42-2.10 (11H, m, 3x C<u>H</u>$_3$ and 2x 5-H); δ_C (DMSO) 136.9 (Ar), 136.8 (2x Ar),

132.9 (Ar), 129.6 (2x Ar), 75.4 (C-2), 68.6 (COH), 49.3 (C-4or C-6), 44.9 (C-4 or C-6), 20.6 (2x CH_3), 20.4 (CH_3), 14.5 (C-5); m/z (EI) 300 (M^+, 1%), 147 (100), 119 (50), 41 (40).

1-(RS)-3-(RS)-α-(RS)-α-(2,6-Difluorophenyl)-1,3-dithiane-1,3-dioxide-2-methanol, (107a), 1-(RS)-3-(RS)-α-(SR)-α-(2,6-Difluorophenyl)-1,3-dithiane-1,3-dioxide-2-methanol, (107b) and 1-(RS)-3-(RS)-α-(RS)-α-(2,6-Difluorophenyl)methylene-1,3-dithiane-1,3-dioxide, (107c).



Dithiane dioxide (**63**) (0.25g, 1.64mmol) was dissolved in pyridine (12.5ml) with warming and then diluted with THF (7.5ml) before cooling to 0 °C, under nitrogen. To this was added a 1.0M solution of NaHMDS in THF (1.97ml, 1.97mmol). Stirring was continued at 0 °C for 0.5hr. 2,6-Difluorobenzaldehye (0.21ml, 1.97mmol) was then added in one portion. Stirring was continued for 1.0min at 0 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (40ml) and aqueous HCl (2M, 4.0ml, 8.2mmol) at 0 C. the solvents were then evaporated under vacuum. Chromatography on silica gel with 25-60% acetone/petrol as the eluant afforded,

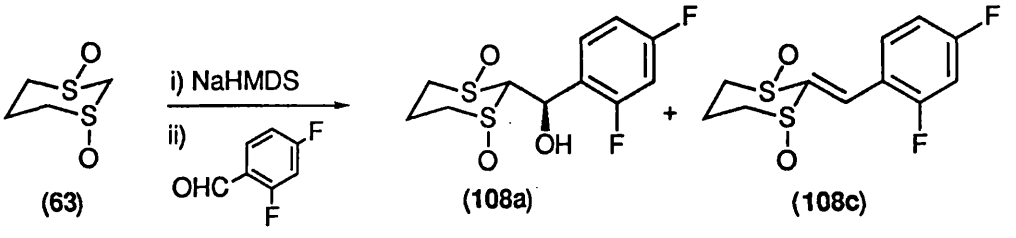
(**107a**) (0.123g, 25%). An analytical sample was recrystallized from ethanol, m.p. 182-6 °C; Rf (acetone) 0.33; (Found: C, 44.7; H, 4.04. Requires for $C_{11}H_{12}F_2O_3S_2$: C, 44.9; H, 4.11%); υ_{max} (Nujol)/ cm^{-1} 3400 (OH), 1010 (S-O); δ_H (DMSO) 7.36 (1H, m, Ar), 7.04 (2H, t, *J* 8.3, Ar), 6.60 (1H, d, *J* 6.8, OH), 5.70 (1H, dd, *J* 9.4 and 6.8, CHOH), 4.28 (1H, d, *J* 9.4, 2-H), 3.40 (1H, m, 4-H), 3.30-3.00 (3H, m, 4-H and 2x 6-H), 2.60-2.15 (2H, m, 2x 5-H); δ_C (DMSO) 161.2 (2C, dd, $J_{C,F}$ 248 and 8.3, 2x *o*Ar), 130.7 (1C, t, $J_{C,F}$ 10.8, Ar), 118.2 (1C, t,

$J_{C,F}$ 16.5, 1-Ar), 112.1 (2C, d, $J_{C,F}$ 24.8, 2x *m*-Ar), 76.8 (C-2), 61.0 (COH), 51.1 (C-4 or C-6), 44.7 (C-4 or C-6), 15.1 (C-5); m/z (CI) 294 (M^+, 30%), 152 (100), 140 (95), 74 (30) and 41 (30).

(**107b**) (0.17g, 35%). An analytical sample was recrystallized from ethanol, m.p. 181-3 °C; Rf (acetone) 0.41; (Found: C, 44.83; H, 4.09. Requires for $C_{11}H_{12}F_2O_3S_2$: C, 44.9; H, 4.11%); υ_{max} (Nujol)/ cm^{-1} 3240 (OH), 995 (S-O); δ_H (DMSO) 7.45 (1H, m, Ar), 7.12 (2H, t, *J* 8.3, Ar), 6.20 (1H, d, *J* 6.0, OH), 5.87 (1H, dd, *J* 7.5 and 6.0, CHOH), 4.50 (1H, d, *J* 7.5, 2-H) 3.50 (1H, m, 4-H), 3.25 (1H, m, 4-H and 2x 6-H), 2.40 (2H, m, 5-H); δ_C (DMSO) 161.0 (2C, dd, $J_{C,F}$ 249 and 8.0 2x *o*-Ar), 131.4 (1C, t, $J_{C,F}$ 10.6, *p*-Ar), 116.8 (1C, t, $J_{C,F}$ 16.5, 1-Ar), 112.4 (d, $J_{C,F}$ 25.2, 2x *m* Ar), 74.8 (C-2), 62.0 (COH), 48.2 (C-4 or C-6), 45.4 (C-4 or C-6), 14.6 (C-5); m/z (CI) 294 (M^+, 40%), 276 (30), 153 (100), 141 (90), 74 (40), 63 (35) and 41 (45).

(**107c**) (0.101g, 22%). An analytical sample was recrystallized from EtOAc/petrol, m.p. 139 °C; Rf (50% acetone/petrol) 0.32; (Found: C, 47.8; H, 3.52. Requires for $C_{11}H_{10}F_2O_2S_2$: C, 47.8; H, 3.65%); υ_{max} (Nujol)/ cm^{-1} 1040 (S-O); δ_H ($CDCl_3$) 7.50-7.30 (2H, Ar and ArCH=), 7.00 (2H, t, *J* 7.5, 2x Ar), 3.75 (1H, m, 4-H), 3.38-2.88 (4H, m, 4-H, 5-H and 2x 6-H), 2.45 (1H, m, 5-H); δ_C ($CDCl_3$) 159.6 (2C, dd, $J_{C,F}$ 251 and 6.1, 2x *o*-Ar), 151.2 (C-2), 132.1 (1C, t, $J_{C,F}$ 10.6, *p* Ar), 122.5 (COH), 111.8 (2C, d, $J_{C,F}$ 23.5, 2x *m*-Ar), 110.1 (1-Ar), 56.2 (C-4 or C-6), 48.3 (C-4 or C-6), 15.1 (C-5); m/z (CI) 276 (M^+, 100%), 228 (90), 170 (35) and 41 (20).

1-(RS)-3-(RS)-α-(RS)-α-(2,4-Difluorophenyl)-1,3-dithiane-1,3-dioxide-2-methanol, (108a) and 1-(RS)-3-(RS)-α-(RS)-α-(2,4-Difluorophenyl)methylene-1,3-dithiane-1,3-dioxide, (108c).



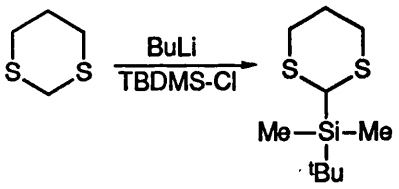
(63) (108a) (108c)

Dithiane dioxide (**63**) (0.15g, 0.985mmol) was dissolved in pyridine (7.5ml) with warming and then diluted with THF (4.5ml) before cooling to 0 °C, under nitrogen. To this was added a 1.0M solution of NaHMDS in THF (1.18ml, 1.18mmol). Stirring was continued at 0 °C for 0.5hr. 2,4-Difluorobenzaldehye (0.13ml, 1.18mmol) was then added in one portion. Stirring was continued for 18 mins at 0 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (25ml) and aqueous HCl (2M, 2.45ml, 4.9mmol) at 0 °C. The solvents were then evaporated under vacuum. Chromatography on silica gel with 25-100% acetone/petrol as the eluant afforded,

(**108a**) (0.099g, 34%). An analytical sample was recrystallized from ethanol, m.p. 198-208 °C; Rf (acetone) 0.33; (Found: C, 44.82; H, 4.07. Requires for $C_{11}H_{12}F_2O_3S_2$: C, 44.9; H, 4.11%); υ_{max} (Nujol)/ cm^{-1} 3260 (OH), 1000 (S-O); δ_H (DMSO) 7.73 (1H, m, Ar), 7.15 (1H, m, Ar), 6.25 (1H, d, *J* 5.6, OH), 5.68 (1H, dd, *J* 5.6 and 4.5, C<u>H</u>OH), 4.03 (1H, d, *J* 4.5, 2-H), 3.50 (1H, m, 4-H), 3.20-2.85 (3H, m, 4-H and 2x 6-H), 2.55 (1H, m, 5-H), 2.23 (1H, m, 5-H); δ_C (DMSO) 162.6 (1C, dd, $J_{C,F}$ 207 and 8.1, Ar-F), 158.7 (1C, dd, $J_{C,F}$ 208 and 12.0, Ar-F), 130.8 (1C, d, $J_{C,F}$ 5.6, Ar), 125.4 (1C, d, $J_{C,F}$ 10.5, quat Ar), 111.8 (1C, d, $J_{C,F}$ 21.2, Ar), 104.1 (1C, t, $J_{C,F}$ 25.9, Ar), 78.0 (C-2), 62.5 (COH), 51.6 (C-4 or C-6), 46.0 (C-4 or C-6), 15.5 (C-5); m/z (CI) 294 (M^+, 15%), 276 (15), 261 (10), 152 (100), 140 (70).

(**108c**) (0.112g, 41%). An analytical sample was recrystallized from EtOAc/petrol, m.p. 190-192 °C; Rf (acetone) 0.64; (Found: C, 47.7; H, 3.56. Requires for $C_{11}H_{10}F_2O_2S_2$: C, 47.8; H, 3.65%); υ_{max} (Nujol)/ cm^{-1} 1040 (S-O); δ_H ($CDCl_3$) 7.50-7.30 (2H, m, Ar and <u>H</u>C=C), 7.07-6.86 (2H, m, 2x Ar), 3.78 (1H, m, 4-H), 3.35-2.80 (4H, m, 2x 6-H, 4-H and 5-H), 2.45 (1H, m, 5-H); δ_C ($CDCl_3$) 164.0 (1C, dd, $J_{C,F}$ 280 and 12.3, Ar-F), 160.0 (1C, dd, $J_{C,F}$ 259 and 8.1, Ar-F), 148.5 (C-2), 132.1 (1C, d, $J_{C,F}$ 9.9, Ar), 127.8 (COH), 116.4 (Ar), 112.2 (1C, dd, $J_{C,F}$ 21.8 and 3.5, Ar), 104.7 (1C, t, $J_{C,F}$ 25.8, Ar), 56.0 (C-4 or C-6), 48.6 (C-4or C-6), 15.0 (C-5); m/z (CI) 277 (M+1, 30%), 228 (80), 170 (100), 125 (80).

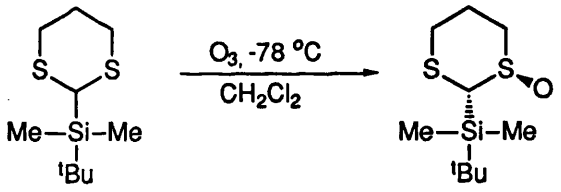
2-*tert*-Butyldimethylsilyl-1,3-dithiane, (115).



(115)

To a stirred solution of 1,3-dithiane (1g, 8.31 mmol) in THF (80 ml), under nitrogen at -78 °C, was added a 1.6M solution of butyllithium in THF (5.7 ml, 9.15 mmol). The mixture was stirred for 20 mins. A solution of *tert*-butyldimethylsilylchloride in THF (80 ml) was then added. The mixture was stirred at -78 °C to room temperature for 3 hours. The reaction mixture was then poured into water and extracted with EtOAc (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to leave a pale yellow oil, (**115**) (1.87g, 96%), δ_H ($CDCl_3$) 3.78 (1H, s, 2-H), 2.87 (2H, m, 2x 4-H), 2.67 (2H, m, 2x 6-H), 2.05 (2H, m, 2x 5-H), 0.96 (9H, s, $(CH_3)_3C$-Si), 0.10 (6H, s, 2x CH_3Si).

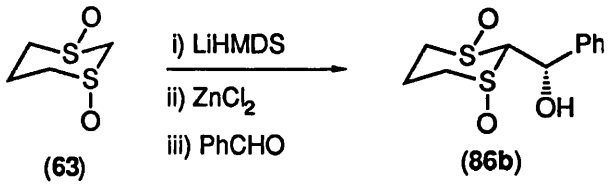
2-*tert*-Butyldimethylsilyl-1,3-dithiane-1-oxide, (116).



(115) **(116)**

Ozone was bubbled through a solution of (**115**) (0.25g, 1.07 mmol) in CH_2Cl_2 at -78 °C for 30 mins. The solvents were then evaporated. Chromatography on silica gel with EtOAc as the eluant afforded a yellow oil which crystallized on standing, (**116**) (0.14g, 52%), δ_H ($CDCl_3$) 3.43 (1H, m, 6-H), 3.26 (1H, s, 2-H), 2.63-2.28 (5H, m, 2x 4-H, 2x 5-H and 6-H), 1.01 (9H, s, $(CH_3)C_3$-Si), 0.29 (3H, s, CH_3Si), 0.21 (3H, s, CH_3Si); m/z (EI) 250 (M^+, 5%), 165 (35), 119 (100), 75 (70).

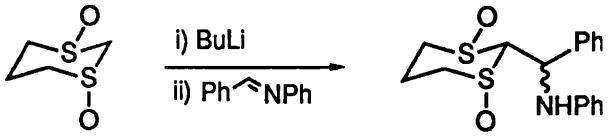
1-(RS)-3-(RS)-α-(SR)-α-Phenyl-1,3-dithiane-1,3-dioxide-2-methanol, (86b).



(63) (86b)

Dithiane dioxide (**63**) (0.2g, 1.31mmol) was dissolved in pyridine (10ml) with warming and then diluted with THF (6ml) before cooling to 0 °C, under nitrogen. To this was added a 1.0M solution of LiHMDS in THF (1.6ml, 1.6mmol). Stirring was continued at 0 °C for 0.5hr. A 1.0M solution of $ZnCl_2$ in THF (2.0ml, 2.0mmol), was then added and stirring cotinued at 0 °C for a further 0.5hr. The mixture was then cooled to -78 °C and benzaldehyde (0.20ml, 2.0mmol) added. Stirring was continued at -78 °C for 45mins. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (35ml) and aqueous HCl (2M, 3.3ml, 6.55mmol) at -78 °C. The solvents were then evaporated under vacuum. Chromatography on silica gel with 50-100% acetone/petrol as the eluant afforded, (**86b**) (0.114g, 34%). An analytical sample was recrystallized from ethanol, m.p. 177-178 °C; Rf (acetone) 0.45; (Found: C, 50.9; H, 5.45. Requires for $C_{11}H_{14}O_3S_2$: C, 51.1; H, 5.46%); υ_{max} (Nujol)/ cm^{-1} 3180 (OH), 975 (S-O); δ_H (DMSO) 7.50-7.25 (5H, m, Ph), 6.19 (1H, d, *J* 4.0, OH), 5.47 (1H, dd, *J* 4.7 and 4.4, C<u>H</u>OH), 4.43 (1H, *J* 4.7, 2-H), 3.46 (1H, m, 4-H), 3.25 (1H, m, 4-H), 3.10 (2H, m, 2x 6-H), 2.35 (2H, m, 2x 5-H); δ_C (DMSO) 141.4 (Ar), 128.2 (2x Ar), 127.8 (Ar), 126.9 (2x Ar), 76.0 (C-2), 67.8 (COH), 48.4 (C-4 or C-6), 14.7 (C-5); m/z (CI) 259 (M+1, 2%), 153 (85), 107 (100), 105 (60).

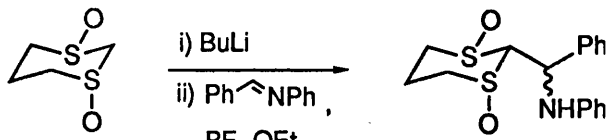
1-(RS)-3-(RS)-α-(RS/SR)-α-Phenyl-1,3-dithiane-1,3-dioxide-2-(*N*-phenyl)methylamine. (141).



(63) (141)

Dithiane dioxide (**63**) (0.05g, 0.328mmol) was dissolved in pyridine (2.5ml) with warming and then diluted with THF (1.5ml) before cooling to 0 °C, under nitrogen. To this was added a 1.0M solution of NaHMDS in THF (0.40ml, 0.40mmol). Stirring was continued at 0 °C for 0.5hr. A solution of benzylideneaniline (0.89g, 0.493mmol) in THF (1ml), was then added and stirring continued at 0 °C-room temperature for 16 hrs. The reaction was then quenched by addition of saturated aqueous NH_4OH solution (1ml). The solvents were then evaporated, azeotroping with toluene (x2). Chromatography on silica gel with 0-50% acetone/EtOAc afforded (**141**) (0.011g, 10%). An analytical sample was recrystallized from acetone, m.p. 248-252 °C; Rf (50% acetone/petrol) 0.18; (Found: C, 61.3; H, 5.59; N, 3.96. Requires for $C_{17}H_{19}NO_2S_2$: C, 61.2; H, 5.74; N, 4.20%); υ_{max} (Nujol)/ cm^{-1} 3360 (N-H), 1050 (S-O); δ_H[136] ($CDCl_3$) 7.59[b] (1H, d, *J* 7.9, NH), 7.49-7.27 (5H, m, Ph), 7.04 (2H, m, Ar), 6.60-6.50 (3H, m, Ar), 6.17[a] (1H, d, *J* 8.6, NH), 5.52[a] (1H, dd, *J* 8.6 and 3.9, CHOH), 5.10[a] (1H, dd, *J* 7.9 and 7,9, CHOH), 4.45[a] (1H, d, *J* 3.9, 2-H), 4.31[b] (1H, d, *J* 7.9, 2-H), 3.55 (1H, m, 4-H), 3.30-2.80 (3H, m, 4-H and 2x 6-H), 2.58 (1H, m, 5-H), 2.30 (1H, m, 5-H); δ_C[137] ($CDCl_3$) 156.0 (Ar), 145.2 (Ar), 129.2 (2x Ar), 128.9 (2x Ar), 128.6 (Ar), 127.2 (2x Ar), 118.3 (Ar), 113.6 (2x Ar), 79.9 (COH), 55.0 (C-2), 52.8 (C-4 or C-6), 47.0 (C-4 or C-6), 14.8 (C-5); m/z (EI) 333 (M^+, 5%), 195 (20), 180 (100), 134 (15).

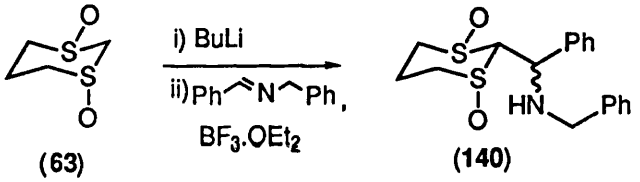
1-(RS)-3-(RS)-α-(RS/SR)-α-Phenyl-1,3-dithiane-1,3-dioxide-2-(*N*-phenyl)methylamine. (141).



(63) (141)

A finely ground powder of (**63**) (0.1g, 0.657mmol) was dissolved in refluxing THF (20ml), under nitrogen. The solution was cooled to 0 °C. To this was added a 1.6M solution of BuLi in THF (0.49ml, 0.79mmol). The mixture was stirred at 0 °C for 5 mins and then cooled to -78 °C. A solution, in THF (2ml), of benzylideneaniline (0.14g, 0.79mmol) precomplexed with $BF_3.OEt_2$ (0.11g, 0.79mmol), was then added, (Prepared by addition of $BF_3.OEt_2$ to a solution of the imine at -78 °C and stirring for 10 mins at -78 °C. Stirring was continued at -78 °C for 2 hrs, then at room temperature for 16 hrs. The reaction was then quenched by addition of saturated aqueous NH_4OH solution (1ml). The solvents were evaporated, azeotroping with toluene (x2). Chromatography on silica gel with 50-100% acetone/petrol afforded (**141**) (0.037g, 17%), see above for analytical data

.1-(RS)-3-(RS)-α-(RS/SR)-α-Phenyl-1,3-dithiane-1,3-dioxide-2-(*N*-benzyl)methylamine, (140).

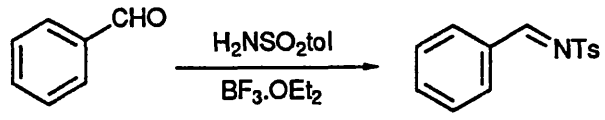


(**63**) (**140**)

Using the method above, dithiane dioxide (**63**) (0.1g, 0.657mmol) was reacted with BuLi (0.5ml, 0.788mmol) and benzylidenebenzylamine (0.15g, 0.788mmol), precomplexed with $BF_3.OEt_2$ (0.11g, 0.788mmol), for 2 hrs at -78 °C. Chromatography on silica gel with 0-50% acetone/EtOAc afforded (**140**) (0.070g, 31%). An analytical sample was recrystallized from acetone/petrol, m.p. 151-158 °C; Rf (acetone) 0.46; (Found: C, 62.3; H, 6.22; N, 3.85. Requires for $C_{18}H_{21}NO_2S_2$: C, 62.2; H, 6.09; N, 4.03%); υ_{max} (Nujol)/ cm^{-1} 3320 (N-H), 1020 (S-O); δ_H[136] ($CDCl_3$) 7.65-7.15 (11H, m, 2x Ph and NH), 4.90[a] (1H, d, *J* 7.0, C<u>H</u>OH), 4.72[b] (1H, d, *J* 10.0, C<u>H</u>OH), 3.95-3.50 (3H and 1H[b], m, 4-H, CH_2Ph and 2-H[b]), 3.40[a] (1H, d, *J* 7.0, 2-H), 3.14-2.50 (4H, m, 4-H, 2x 6-H and 5-H), 2.30 (1H, m, 5-H); δ_C[136] ($CDCl_3$) 139.5[b] (Ar), 139.3[a] (Ar), 138.1[b] (Ar), 137.7[a] (Ar), 129.1[c] (Ar), 129.0[c] (Ar), 128.8[c] (Ar), 128.7[c] (Ar), 128.5[c] (Ar), 128.3[c] (Ar), 128.2[c] (Ar), 127.8[c] (Ar), 127.0[c] (Ar), 80.4[a] (COH), 79.2[b] (COH), 62.6[b] (C-2), 58.9[a] (C-2), 51.2[b] (C-4, C-6 or CH_2Ph), 51.0[a] (C-4, C-6 or

CH_2Ph), 50.1 (C-4, C-6 or CH_2Ph), 45.8[a] (C-4, C-6 or CH_2Ph), 45.6[b] (C-4, C-6 or CH_2Ph), 14.3 (C-5); m/z (EI) 347 (M^+, 10%), 330 (55), 256 (60), 238 (30), 208 (100).

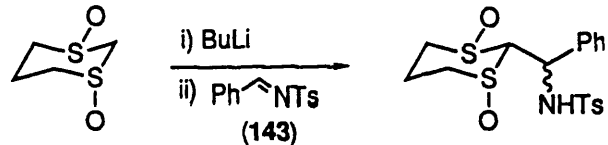
N-Benzylidenetoluene-*p*-sulphonamide, (143).



(143)

Benzaldehyde (5g, 47.1mmol), *p*-toluenesulphonamide (8.07g, 47.1mmol) and $BF_3.OEt_2$ were reacted in toluene (300ml) according to the procedure of Procter[102], to give (**143**) (8.60g, 70%), m.p. 103 °C (lit.,[102] 104 °C); δ_H ($CDCl_3$) 9.03 (1H, s, PhC<u>H</u>=N), 7.91 (4H, m, Ar), 7.62 (1H, m, Ar), 7.48 (2H, m, Ar), 7.34 (2H, m, Ar), 2.43 (3H, s, C<u>H</u>$_3$).

1-(RS)-3-(RS)-α-(RS/SR)-α-Phenyl-1,3-dithiane-1,3-dioxide-2-(*N*-toluene-*p*-sulphonyl)methylamine, (144).

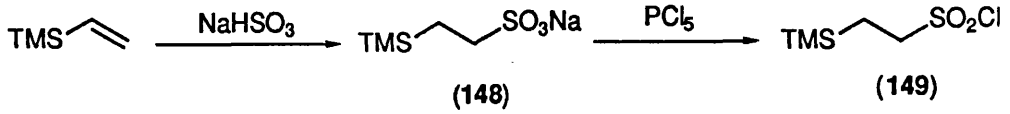


(63) **(144)**

Dithiane dioxide (**63**) (1.0g, 6.57mmol) was dissolved in pyridine (50ml) with warming and then diluted with THF (30ml) before cooling to 0 °C, under nitrogen. To this was added a 1.0M solution of NaHMDS in THF (7.90ml, 7.90mmol). Stirring was continued at 0 °C for 0.5hr. A solution of (**143**) (2.0g, 7.90mmol) in THF (5ml), was then added and stirring continued at 0 °C for 15 mins. The reaction was then quenched by addition of saturated aqueous NH_4OH solution (2ml). The solvents were evaporated, azeotroping with toluene (x2). Chromatography on silica gel with 25-100% acetone/EtOAc afforded (**144**) (1.80g, 66%). An analytical sample was recrystallized from methanol, m.p. 219 °C; Rf (acetone) 0.65; (Found: C, 51.9; H, 5.17; N, 3.16. Requires for $C_{18}H_{21}NO_4S_3$: C, 52.5; H, 5.14; N, 3.40%); υ_{max} (Nujol)/ cm^{-1} 3140 (N-H), 1025 (S-O); δ_H[136] (DMSO) 8.70[b] (1H, d, *J* 8.1, NH), 7.86[a] (1H, d, *J* 9.5, NH), 7.53-7.13 (9H, m, Ar), 5.46[a] (1H, dd, *J* 9.5 and 4.4, C<u>H</u>NH), 5.00[b] (1H, dd, *J* 8.1 and 8.1, C<u>H</u>NH), 4.24[a] (1H, d, *J* 4.4, 2-H), 4.21[b] (1H, d, *J* 8.1, 2-H), 3.55 (1H, m, 4-H),

3.24-2.80 (3H, m, 4-H and 2x 6-H), 2.60-2.30 (2H, m, 2x 5-H), 2.28 (3H, s, $C\underline{H}_3$); δ_C[137] (DMSO) 142.9 (Ar), 138.4 (Ar), 137.4 (Ar), 129.5 (2x Ar), 128.7 (2x Ar), 128.0 (Ar), 127.7 (2x Ar), 127.2 (2x Ar), 76.7 (C-2), 54.9 (COH), 50.3 (C-4 or C-6), 45.7 (C-4 or C-6), 21.4 (CH_3), 15.1 (C-5); m/z (EI) 411 (M^+, 20%), 273 (90), 260 (100), 208 (65).

β-Trimethylsilylethanesulphonyl Chloride, (149).

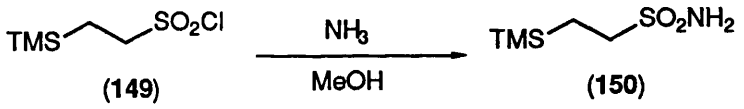


(148) (149)

According to Weinrebs' procedure[94], vinyl trimethylsilane (12.5g, 0.125mol), sodium bisulphite (25.4g, 0.243mol) and ^{t}butyl perbenzoate (0.49g, 2.5mmol) were reacted in methanol (50ml) and water (50ml) to give, **sodium-β-trimethylsilylethanesulphonate, (148)** (15.5g, 61%), δ_H (DMSO) 2.30 (2H, m, $NaSO_3C\underline{H}_2$), 0.79 (2H, m, $C\underline{H}_2Si(CH_3)_3$), -0.05 (9H, s, $Si(C\underline{H}_3)_3$).

The crude product (**148**) (15.5g, 75.6mmol) and phosphorous pentachloride (47.2g, 0.227mol) were then reacted in chloroform (50ml) to give unpurified (**149**) (16.7g, >100%), δ_H ($CDCl_3$) 3.60 (2H, m, $ClSO_2C\underline{H}_2$), 1.30 (2H, m, $C\underline{H}_2Si(CH_3)_3$), 0.10 (9H, s, $Si(C\underline{H}_3)_3$).

β-Trimethylsilylethanesulphonamide, (150).

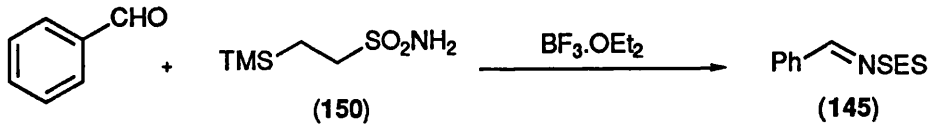


(149) (150)

To a 2M solution of ammonia in methanol, at 0 °C, under nitrogen, was added crude (**149**) (15.0g, 67.9mmol). The mixture was stirred at 0 °C for 90 mins. The solvents were then evaporated and the residue portioned between aqueous saturated $NaHCO_3$ solution and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (x2). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 25-50% EtOAc/petrol as the eluant afforded (**150**) (2.61g, 21%),

Rf (50% EtOAc/petrol) 0.40; δ_H ($CDCl_3$) 4.65 (2H, br.s, NH_2), 3.05 (2H, m, $H_2NSO_2C\underline{H}_2$), 1.10 (2H, m, $C\underline{H}_2Si(CH_3)_3$), 0.06 (9H, s, $Si(C\underline{H}_3)_3$).

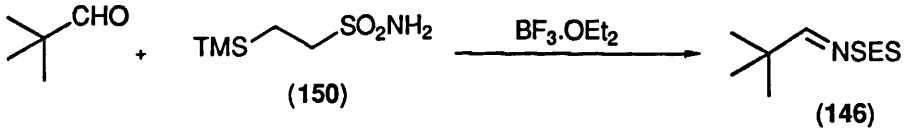
N-Benzylidene-β-Trimethylsilylethanesulphonamide, (145).



(150) (145)

Benzaldehyde (0.88g, 8.27mmol), (**150**) (1.5g, 8.27mmol), and $BF_3.OEt_2$ (0.12g, 0.827mmol) were heated under reflux in toluene (50ml) in a Dean-Stark apparatus, under nitrogen, for 6 hrs. After cooling, the reaction mixture was poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 5-30% EtOAc/petrol as the eluant afforded (**145**) (1.45g, 65%), Rf (20% EtOAc/petrol) 0.50; δ_H ($CDCl_3$) 9.06 (1H, s, PhC<u>H</u>=N), 7.99 (2H, m, Ar), 7.68 (1H, m, Ar), 7.56 (2H, m, Ar), 3.16 (2H, m, $SO_2C\underline{H}_2$), 1.07 (2H, m, $C\underline{H}_2Si(CH_3)_3$), 0.06 (9H, s, $Si(C\underline{H}_3)_3$).

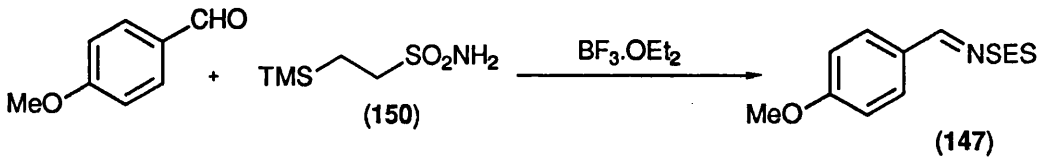
N-(2,2-Dimethylpropylidene)-β-Trimethylsilylethanesulphonamide, (146).



(150) (146)

Trimethylacetaldehyde (1.2g, 13.8mmol), (**150**) (0.5g, 2.76mmol), and $BF_3.OEt_2$ (0.039g, 0.276mmol) were heated under reflux in toluene (15ml) for 1 hr. After cooling, the reaction mixture was poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 5-20% EtOAc/petrol as the eluant afforded (**146**) (0.157g, 20%), Rf (20% EtOAc/petrol) 0.63; δ_H ($CDCl_3$) 8.48 (1H, s, C<u>H</u>=N), 3.06 (2H, m, $C\underline{H}_2SO_2N$), 1.19 (9H, s, $(C\underline{H}_3)_3C$), 0.99 (2H, m, $C\underline{H}_2SiMe_3$), 0.06 (9H, s, $Si(C\underline{H}_3)_3$).

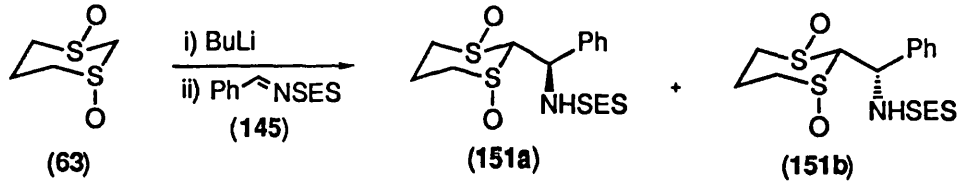
N-(*p*-Methoxy)-Benzylidene-β-Trimethylsilylethanesulphonamide, (147).



(150) (147)

p-Anisaldehyde (0.75g, 5.51mmol), (**150**) (0.5g, 2.76mmol), and $BF_3.OEt_2$ (0.039g, 0.276mmol) were heated under reflux in toluene (15ml) in a Dean-Stark apparatus, under nitrogen, for 5 hrs. After cooling, the reaction mixture was poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 5-20% EtOAc/petrol as the eluant afforded (**147**) (0.577g, 70%), Rf (20% EtOAc/petrol) 0.40; δ_H ($CDCl_3$) 8.93 (1H, s, ArC<u>H</u>=N), 7.95 (2H, d, *J* 9.0, Ar), 7.00 (2H, d, *J* 9.0, Ar), 3.91 (3H, s, OCH_3), 3.13 (2H, m, $C\underline{H}_2SO_2N$), 1.06 (2H, m, $C\underline{H}_2SiMe_3$), 0.05 (9H, s, $Si(C\underline{H}_3)_3$).

<u>1-(RS)-3-(RS)-α-(RS)-α-Phenyl-1,3-dithiane-1,3-dioxide-2-(*N*-β-trimethylsilylethanesulphonyl)methylamine, (151a)</u> and <u>1-(RS)-3-(RS)-α-(SR)-α-Phenyl-1,3-dithiane-1,3-dioxide-2-(*N*-β-trimethylsilylethanesulphonyl)methylamine, (151b).</u>



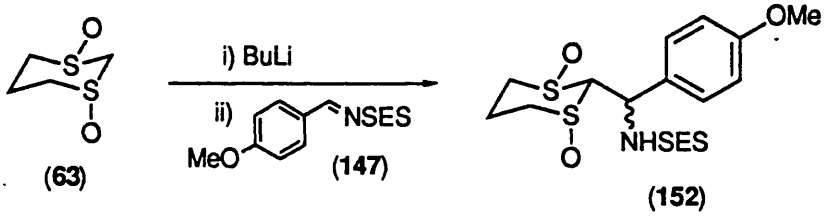
(63) (151a) (151b)

Dithiane dioxide (**63**) (0.1g, 0.657mmol) was dissolved in pyridine (5ml) with warming and then diluted with THF (3ml) before cooling to 0 °C, under nitrogen. To this was added a 1.0M solution of NaHMDS in THF (0.79ml, 0.79mmol). Stirring was continued at 0 °C for 0.5hr. A solution of (**145**) (0.194g, 0.720mmol) (freshly recrystallized from EtOAc/petrol), in THF (1ml), was then added and stirring continued at 0 °C for 10 mins. The reaction was then quenched by addition of saturated aqueous NH_4OH solution (1ml). The solvents were then evaporated, and the residue portioned between aqueous saturated $NaHCO_3$ solution and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (x2). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 25-100% acetone/petrol afforded (**151a**), as a single diastereomer (0.030g, 11%). An analytical sample was recrystallized from EtOAc, m.p. 163-167 °C; Rf (50% acetone/petrol) 0.40; (Found: C, 46.1; H, 6.59; N, 3.03. Requires for $C_{16}H_{27}NO_4S_3Si$: C, 45.6; H, 6.45; N, 3.32%); υ_{max} (Nujol)/ cm^{-1} 3180 (N-H), 1030 (S-O); δ_H ($CDCl_3$) 7.66-7.30 (5H, m, Ph),

6.62 (1H, d, *J* 9.8, NH), 5.70 (1H, dd, *J* 9.8 and 5.3, CHNH), 3.68 (1H, m, 4-H), 3.60 (1H, d, *J* 5.3, 2-H), 3.21-2.52 (6H, m, 4-H, 2x 6-H, 5-H and CH_2SO_2NH), 2.38 (1H, m, 5-H), 1.04 (2H, m, $CH_2Si(CH_3)_3$), -0.04 (9H, s, $Si(CH_3)_3$).; δ_C ($CDCl_3$) 137.2 (Ar), 129.2 (2x Ar), 128.8 (Ar), 127.0 (2x Ar), 78.1 (COH), 55.4 (C-2), 50.4 (C-4, C-6 or CH_2SO_2NH), 50.3 (C-4, C-6 or CH_2SO_2NH), 46.3 (C-4, C-6 or CH_2SO_2NH), 14.7 (C-5), 10.3 (CH_2SiMe_3), -2.0 ($Si(CH_3)_3$); m/z (EI) 421 (M^+, 40%), 406 (35), 270 (80), 224 (75), 208 (100).

Continued elution of the column also afforded (**151b**), as a single diastereomer (0.045g, 16%). An analytical sample was recrystallized from methanol, m.p. 243 °C; Rf (50% acetone/petrol) 0.25; (Found: C, 45.8; H, 6.64; N, 3.14. Requires for $C_{16}H_{27}NO_4S_3Si$: C, 45.6; H, 6.45; N, 3.32%); υ_{max} (Nujol)/ cm^{-1} 3400 (N-H), 1030 (S-O); δ_H (DMSO) 8.20 (1H, br.s, NH), 7.55 (2H, m, Ar), 7.36 (3H, m, Ar), 5.14 (1H, d, *J* 9.0, CHNH), 4.26 (1H, d, *J* 9.0, 2-H), 3.58 (1H, m, 4-H), 3.35-3.05 (5H, m, 4-H, 2x 6-H and CH_2SO_2NH), 2.50-2.17 (2H, m, 2x 5-H), 0.65 (2H, m, CH_2SiMe_3), -0.20 (9H, s, $Si(CH_3)_3$); δ_C (DMSO) 138.0 (Ar), 128.9 (2x Ar), 128.5 (Ar), 127.8 (2x Ar), 77.3 (C-2), 56.5 (COH), 50.9 (C-4, C-6 or CH_2SO_2NH), 49.0 (C-4, C-6 or CH_2SO_2NH), 44.5 (C-4, C-6 or CH_2SO_2NH), 14.3 (C-5), 10.9 (CH_2SiMe_3), -1.7 ($Si(CH_3)_3$); m/z (EI) 421 (M^+, 20%), 405 (10), 270 (60), 222 (100), 206 (55).

1-(RS)-3-(RS)-α-(RS)-α-(4-Methoxyphenyl)-1,3-dithiane-1,3-dioxide-2-(*N*-β-trimethylsilylethanesulphonyl)methylamine, (152).

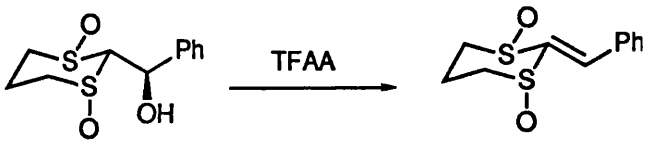


(63) (147) (152)

Dithiane dioxide (**63**) (0.16g, 1.05mmol) was dissolved in pyridine (8ml) with warming and then diluted with THF (5ml) before cooling to 0 °C, under nitrogen. To this was added a 1.0M solution of LiHMDS in THF (1.26ml, 1.26mmol). Stirring was continued at 0 °C for 0.5hr. A solution of (**147**) (0.35g, 1.16mmol), in THF (1ml), was then added and stirring continued at 0 C for 1 hr. The reaction was then quenched by addition of saturated aqueous

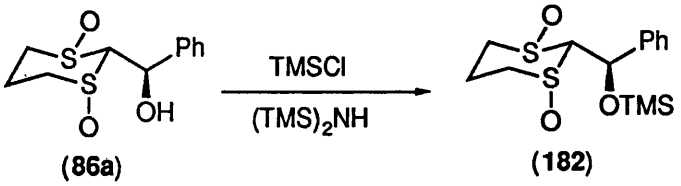
NH_4OH solution (1ml). The solvents were then evaporated. Chromatography on silica gel with 25-100% acetone/petrol afforded (**152**), as a mixture of diastereomers, (0.197g, 41%). An analytical sample was recrystallized from methanol, m.p. 232 °C; Rf (acetone) 0.70; (Found: C, 45.2; H, 6.45;N, 2.94. Requires for $C_{17}H_{29}NO_5S_3Si$: C, 45.2; H, 6.47; N, 3.10%); υ_{max} (Nujol)/ cm^{-1} 3100 (N-H), 1000 (S-O); δ_H[136] (DMSO) 8.13[a] (1H, br,s, NH), 7.45 (2H, m, Ar), 7.24[b] (1H, br.s, NH), 6.98 (2H, m, Ar), 5.32[b] (1H, d, *J* 5.6, C<u>H</u>NH), 5.07[a] (1H, d, *J* 8.3, C<u>H</u>NH), 4.29[b] (1H, d, *J* 5.6, 2-H), 4.21[a] (1H, d, *J* 8.3, 2-H), 3.74 (3H, s, OCH_3), 3.59 (1H, m, 4-H), 3.26-2.13 (7H, m, 4-H, 2x 6-H, 2x 5-H and $C\underline{H}_2SO_2N$), 0.80[b] (2H, m, $C\underline{H}_2SiMe_3$), 0.61[a] (2H, m, $C\underline{H}_2SiMe_3$), -0.09[b] (9H, s, $Si(C\underline{H}_3)_3$), -0.19[a] (9H, s, $Si(C\underline{H}_3)_3$); δ_C[136] (DMSO) 159.8[a] (Ar, <u>C</u>OMe), 159.5[b] (Ar, <u>C</u>OMe), 130.6[b] (Ar), 130.3[a] (2x Ar), 129.5[a] (Ar), 129.1[b] (2x Ar), 114.5[b] (Ar), 114.2[a] (Ar), 77.3[a] (COH), 76.7[b] (COH), 56.1[a] (C-2), 55.6 ($O\underline{C}H_3$), 54.3[b] (C-2), 49.8[a] (C-4, C-6 or $\underline{C}H_2SO_2$), 49.7[b] (C-4, C-6 or $\underline{C}H_2SO_2$), 49.5 (C-4, C-6 or $\underline{C}H_2SO_2$), 45.6[b] (C-4, C-6 or $\underline{C}H_2SO_2$), 44.8[a] (C-4, C-6 or $\underline{C}H_2SO_2$), 15.2[b] (C-5), 14.3[a] (C-5), 10.1[b] ($\underline{C}H_2SiMe_3$), 10.0 ($\underline{C}H_2SiMe_3$), -1.6 ($Si(\underline{C}H_3)_3$), -1.7 ($Si(\underline{C}H_3)_3$); m/z (EI) 451 (M^+, 5%), 270 (70), 238 (100), 223 (45).

1-(RS)-3-(RS)-2-Phenylmethylene-1,3-dithiane-1,3-dioxide, (86c).



The alcohol (**86a**) (0.081g, 0.314 mmol) was suspended in pyridine (5ml) in a dried flask under nitrogen, and cooled to -15 °C. Trifluoroaceticanhydride (0.049ml, 0.345mmol) was then added and stirring continued at -15 °C-room temperature for 16hrs. The mixture was poured into water and extracted with CH_2Cl_2 (x3). Combined organics extracts were dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 50% acetone/petrol as eluant afforded (**86a**) (0.049g, 65%). An analytical sample was recrystallized from EtOAc/petrol, m.p. 157 °C; Rf (acetone) 0.52; (Found: C, 55.1; H, 5.07. Requires for $C_{11}H_{12}O_2S_2$: C, 55.0; H, 5.03%); υ_{max} (Nujol)/ cm^{-1} 3120 and 1080 (S-O); δ_H ($CDCl_3$) 7.52 (1H, s, CHOH), 7.44 (5H, s, Ar), 3.73 (1H, dm, *J* 12.5, 4-H_{eq}), 3.29 (1H, dm, *J* 15.8, 4-H_{ax}), 3.15 (1H, m, 6-H), 2.97-2.77 (2H, m, 6-H and 5-H), 2.43 (1H, dm, *J* 18.7, 5-H); δ_C ($CDCl_3$) 146.0 (Ar), 136.1 (Ar), 132.0 (C-2), 130.3 (2x Ar), 130.2 (2x Ar), 128.9 (CHPh), 56.1 (C-4 or C-6), 48.8 (C-4 or C-6), 14.9 (C-5); m/z (EI) 240 (M^+, 10%), 192 (100), 175 (45), 134 (40), 57 (40), 41 (40).

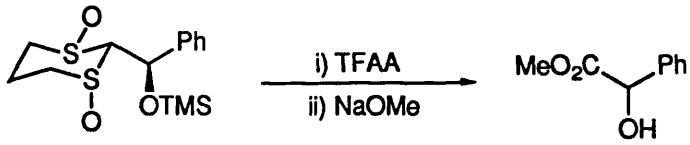
1-(RS)-3-(RS)-α-(RS)-α-Phenyl-1,3-dithiane-1,3-dioxide-2-trimethylsilyloxymethane, (182).



The alcohol (**86a**) (0.050g, 0.193 mmol) was suspended in pyridine (5ml) in a dried flask under nitrogen, and cooled to 0 °C. Chlorotrimethylsilane (0.1ml, 0.79mmol) and 1,1,1,3,3,3-hexamethyldisilazane (0.2ml, 1.74mmol) were added and the mixture stirred at 0 °C-room temperature for 16 hrs. The mixture was poured into water and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give

(**182**) (0.047g, 73%). An analytical sample was recrystallized from EtOAc/petrol, m.p. 152-153 °C; Rf (acetone) 0.57; (Found: C, 50.2; H, 6.61. Requires for $C_{14}H_{22}O_3S_2Si$: C, 50.9; H, 6.71%); υ_{max} (Nujol)/ cm^{-1} 1025 (S-O); δ_H ($CDCl_3$) 7.49 (2H, m, Ar), 7.37 (3H, m, Ar), 5.68 (1H, d, *J* 4.4, C<u>H</u>OH), 3.68 (1H, m, 4-H_{eq}), 3.32 (1H, d, *J* 4.4, 2-H), 3.10 (1H, dt, *J* 15.0 and 3.0, 4-H_{ax}), 2.90 (2H, m, 2x 6-H), 2.56 (1H, m, 5-H), 2.35 (1H, m, 5-H), 0.14 (9H, s, 3x CH_3, TMS); δ_C ($CDCl_3$) 140.0 (Ar), 128.5 (Ar), 128.2 (2x Ar), 126.5 (2x Ar), 82.2 (C-2), 69.4 (COTMS), 51.2 (C-4 or C-6), 46.0 (C-4 or C-6), 14.3 (C-5), -0.2 (3x CH_3, TMS); m/z (EI) 330 (M^+, 60%), 192 (35), 176 (100), 73 (25).

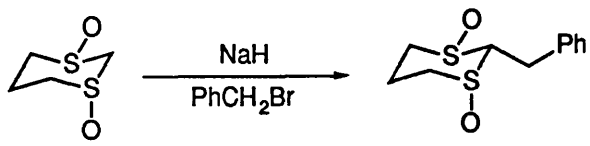
<u>(RS)-Methyl mandelate, (186).</u>



(182) (186)

Pyridine (0.24ml, 3.03mmol) was added to a stirred solution of (**182**) (0.25g, 0.756mmol) in dry CH_2Cl_2 (5ml) under nitrogen. The solution was cooled to 0 °C and trifluoroacetic anhydride (0.12ml, 0.832mmol) added. Stirring was continued at 0 °C for 15 mins. Sodium methoxide (0.2g, 3.78mmol) was then added as a solution in methanol (3ml). Stirring was continued at 0 °C for a further 15 mins. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with EtOAc (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 5-15% EtOAc/petrol as the eluant afforded **methyl mandelate** (**186**) (0.077g, 48%), m.p. 50-53 °C (lit.,[134] 51-54 °C); δ_H ($CDCl_3$) 7.42-7.30 (5H, m, Ph), 5.18 (1H, s, C<u>H</u>OH), 3.75 (3H, s, CO_2<u>Me</u>), 3.30 (1H, br s, OH).

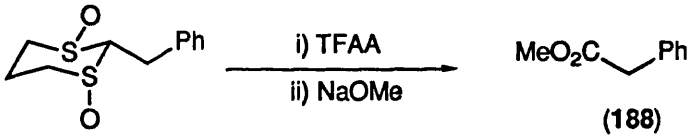
<u>1-(RS)-3-(RS)-2-Benzyl-1,3-dithiane-1,3-dioxide, (187).</u>



(63) (187)

To a slurry of NaH (97%) (0.51g, 21.3mmol) in DMF (10ml), at 0 °C under nitrogen, was added a solution of (**63**) (2.5g, 16.4mmol) in DMF (60ml). Stirring was continued at 0 °C for 0.5 hr. Benzyl bromide (2.54ml, 21.3mmol) was then added and stirring contiued at 0 °C for 1 hr. Water was then added (3ml) and the solvents evaporated under high vacuum. The residue was portioned between water and EtOAc and the layers separated. The aqueous phase was extracted with EtOAc (x2). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 60-100% acetone/petrol afforded (**187**) (2.95g, 76%). An analytical sample was recrystallized from EtOAc, m.p. 144 °C; Rf (acetone) 0.46; (Found: C, 54.1; H, 5.85. Requires for $C_{11}H_{14}O_2S_2$: C, 54.5; H, 5.82%); υ_{max} (Nujol)/ cm^{-1} 1010 (S-O); δ_H (DMSO) 7.34 (5H, m, Ph), 4.29 (1H, dd, *J* 11.5 and 4.2, 2-H), 3.53 (2H, m, $C\underline{H}_2Ph$), 3.30-2.90 (4H, m, 2x 4-H and 2x 6-H), 2.48 (1H, m, 5-H), 2.26 (1H, m, 5-H); δ_C (DMSO) 136.1 (Ar), 129.5 (2x Ar), 128.7 (2x Ar), 73.9 (C-2), 49.8 (C-4 or C-6), 30.0 ($\underline{C}H_2Ph$), 15.2 (C-5); m/z (EI) 242 (M^+, 100%), 135 (40), 123 (35), 104 (50), 91 (40).

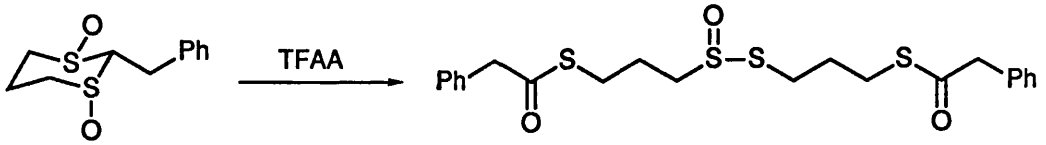
Methyl phenyl acetate, (188).



(**187**) (**188**)

Pyridine (0.27ml, 3.30mmol) was added to a stirred solution of (**187**) (0.20g, 0.825mmol) in dry CH_2Cl_2 (5ml) under nitrogen. The solution was cooled to 0 °C and trifluoroacetic anhydride (0.13ml, 0.908mmol) added. Stirring was continued at 0 °C for 15 mins. Sodium methoxide (0.22g, 4.13mmol) was then added as a solution in methanol (3ml). Stirring was continued at 0 C for a further 15 mins. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with EtOAc (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 1% EtOAc/petrol as the eluant afforded methyl phenyl acetate (**188**) (0.072g, 58%) as a colourless oil. δ_H ($CDCl_3$) 7.29 (5H, m, Ar), 3.68 (3H, s, $CO_2\underline{Me}$), 3.62 (2H, s, $PhC\underline{H}_2$).[135]

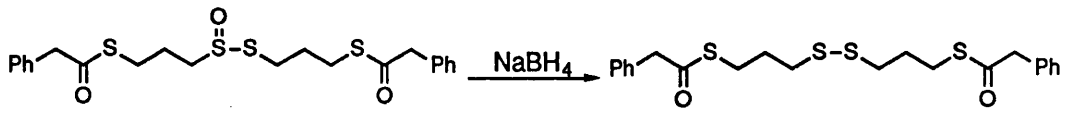
Bis-(3-phenylacetylthio)propyl thiosulphinate, (189).



(187) (189)

Pyridine (1.33ml, 16.5mmol) was added to a stirred solution of (**187**) (1.0g, 4.13mmol) in dry CH_2Cl_2 (25ml) under nitrogen. The solution was cooled to 0 °C and trifluoroacetic anhydride (0.95g, 4.54mmol) added. Stirring was continued at 0 °C for 15 mins.The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 15-30% EtOAc/petrol as the eluant afforded (**189**) (0.74g, 77%). An analytical sample was recrystallized from EtOAc/petrol, m.p. 50 °C; Rf (50% EtOAc/petrol) 0.69; (Found: C, 56.6; H, 5.69. Requires for $C_{22}H_{26}O_3S_4$: C, 56.6; H, 5.62%); υ_{max} ($CHCl_3$)/ cm^{-1} 1660s (C=O), 1060, 990, 700; δ_H ($CDCl_3$) 7.30 (10H, m, 2x Ph), 3.83 (2H, s, $C\underline{H}_2Ph$), 3.89 (2H, s, $C\underline{H}_2Ph$), 3.11 (4H, m, $C\underline{H}_2CH_2CH_2$), 2.97 (4H, m, 2x $CH_2CH_2C\underline{H}_2$), 2.07 (4H, 2x $CH_2C\underline{H}_2CH_2$); δ_C ($CDCl_3$) 196.9 (2x C=O), 133.4 (Ar), 133.2 (Ar), 129.5 (4x Ar), 128.7 (4x Ar), 127.4 (2x Ar), 54.5 (CH_2), 50.5 (2x CH_2), 31.6 (CH_2), 30.5 (CH_2), 27.8 (CH_2), 27.6 (CH_2), 23.6 (CH_2); m/z ((+)FAB) 467 (M+1, 1.5%), 225 (20), 119 (60), 91 (100).

Bis-(3-phenylacetylthio)propyl disulphide, (194).

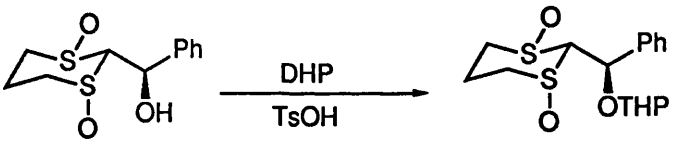


(189) (194)

The thiosulphinate (**189**) (0.1g, 0.214mmol) was suspended in methanol (1ml) and stirred under nitrogen at room temperature. Sodium borohydride (25mg, 0.661mmol) was then added and stirring continued for 0.5 hr. The reaction mixture was then poured into water and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 5-20% EtOAc/petrol as the eluant afforded a pale yellow gum, (**194**) (0.05g, 52%). Rf (20% EtOAc/petrol) 0.79; υ_{max}

(Liq. film)/ cm^{-1} 2920, 1685 (C=O), 1020 (S-O); δ_H ($CDCl_3$) 7.30 (10H, m, 2x Ph), 3.81 (4H, s, 2x $C\underline{H}_2Ph$), 2.93 (4H, t, *J* 7.2, 2x $C\underline{H}_2CH_2CH_2$), 2.64 (4H, t, *J* 7.2, 2x $CH_2CH_2C\underline{H}_2$), 1.92 (4H, quintet, *J* 7.2, 2x $CH_2C\underline{H}_2CH_2$); δ_C ($CDCl_3$) 196.6 (2x C=O), 133.1 (2x Ar), 129.0 (4x Ar), 128.2 (4x Ar), 126.9 (2x Ar), 50.0 (2x CH_2), 36.8 (2x CH_2), 28.9 (2x CH_2), 27.3 (2x CH_2); m/z (EI) 450 (M^+, 2%), 91 (100).

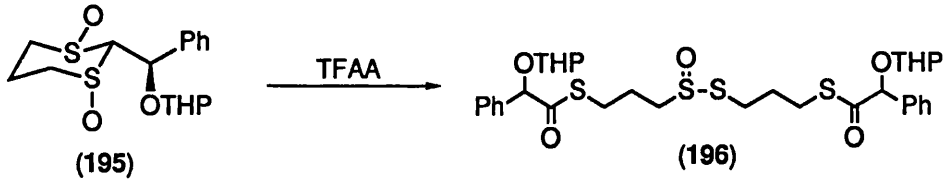
1-(RS)-3-(RS)-α-(RS)-α-Phenyl-1,3-dithiane-1,3-dioxide-2-[(tetrahydro-2*H*-pyran-2-yl)oxy]methane.(195).



(86a) (195)

The alcohol (**86a**) (0.416g, 1.61mmol) was suspended in dry CH_2Cl_2 (10ml) under nitrogen at 0 °C. Dihydropyran (0.73ml, 8.05mmol) and tosic acid (12mg, 0.064mmol) were added and stirring continued at 0 °C for 2 hrs. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 25-100% acetone/petrol as the eluant afforded (**195**) (0.46g, 83%). An analytical sample was recrystallized from EtOAc/petrol, m.p. 153-164 °C; Rf (acetone) 0.48; (Found: C, 55.7; H, 6.43. Requires for $C_{16}H_{22}O_4S_2$: C, 56.1; H, 6.48%); υ_{max} (Nujol)/ cm^{-1} 1435, 1020 (S-O); δ_H [136]($CDCl_3$) 7.56-7.33 (5H, Ar), 5.69[a] (1H, d, *J* 4.8, C$\underline{H}$OH), 5.59[b] (1H, d, *J* 4.6, C$\underline{H}$OH), 5.14[b] (1H, t, *J* 3.1, OC$\underline{H}$O), 4.66[a] (1H, t, *J* 3.5, OC$\underline{H}$O), 4.17[a] (1H, m, O(HC$\underline{H}$)CH_2), 3.68 (2H, m, O($\underline{H}$CH)CH_2 and 4-H), 3.48[b] (1H, d, *J* 4.6, 2-H), 3.43[a] (1H, d, *J* 4.8, 2-H), 3.32[b] (1H, m, O(HC$\underline{H}$)CH_2), 3.15 (1H, dm, *J* 13.9, 4-H), 2.93 (2H, m, 2x 6-H), 2.66 (1H, m, 5-H), 2.48 (1H, m, 5-H), 2.08-1.40 (6H, m, 3x CH_2); δ_C[137]($CDCl_3$) 136.7 (Ar), 128.9 (2x Ar), 127.7 (2x Ar), 126.9 (Ar), 94.3 (O$\underline{C}$HO), 80.9 (C-2), 70.8 (COH), 61.6 (CH_2), 50.9 (CH_2), 45.7 (CH_2), 30.0 (CH_2), 25.4 (CH_2), 18.2 (CH_2), 14.0 (CH_2); m/z (EI) 342 (M^+, 1%), 193 (55), 85 (100).

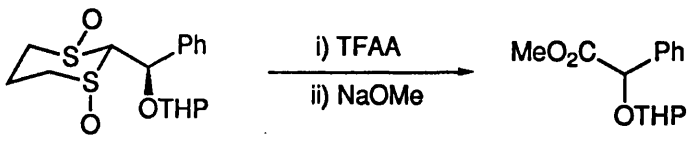
Bis-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]phenylacetylthio]propyl thiosulphinate, (196).



(195) (196)

Pyridine (0.14ml, 1.75mmol) was added to a stirred solution of (**195**) (0.15g, 0.438mmol) in dry CH_2Cl_2 (5ml) under nitrogen. The solution was cooled to 0 °C and trifluoroacetic anhydride (0.10g, 0.482mmol) added. Stirring was continued at 0 °C for 15 mins. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 15-30% EtOAc/petrol as the eluant afforded (**196**) as a pale yellow gum (0.101g, 69%) Rf (50% EtOAc/petrol) 0.6; υ_{max} (Liq. film)/ cm^{-1} 2920, 1730 (w), 1670 (s) (C=O), 1450; δ_H[136] ($CDCl_3$) 7.51-7.30 (10H, m, 2x Ph), 5.28[a] (1H, s, α-H), 5.25[b] (1H, s, α-H), 4.92[a] (1H, m, OC<u>H</u>O), 4.13[b] (1H, m, OC<u>H</u>O), 3.98[b] (1H, m, O<u>H</u>CHCH$_2$), 3.60 (1H, m, OHC<u>H</u>CH$_2$), 3.45[a] (1H, m, O<u>H</u>CHCH$_2$), 3.10 (4H, m, 2x C<u>H</u>$_2$S), 2.94 (4H, m, 2x C<u>H</u>$_2$S), 2.16-1.44 (16H, m, 2x SCH$_2$C<u>H</u>$_2$CH$_2$S and 2x CH$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$); δ_C ($CDCl_3$) 201.55 (C=O), 201.42 (C=O), 199.99 (C=O), 199.87 (C=O), 136.71 (quat., Ar), 136.62 (quat., Ar), 136.23 (quat., Ar), 128.70 (CH, Ar), 128.64 (CH, Ar), 128.57 (CH, Ar), 128.44 (CH, Ar), 128.31 (CH, Ar), 127.4 (CH, Ar), 126.59 (CH, Ar), 98.02 (O<u>C</u>HO), 95.39 (O<u>C</u>HO), 81.93 (COTHP), 81.57 (COTHP), 61.95 (CH_2), 61.89 (CH_2), 54.46 (CH_2), 54.39 (CH_2), 31.66 (CH_2), 30.36 (CH_2), 30.03 (CH_2), 29.84 (CH_2), 29.61 (CH_2), 26.73 (CH_2), 26.50 (CH_2), 25.27 (CH_2), 25.10 (CH_2), 23.45 (CH_2), 18.42 (CH_2); m/z ((-)FAB) 665 (M-1, 10%), 251 (100).

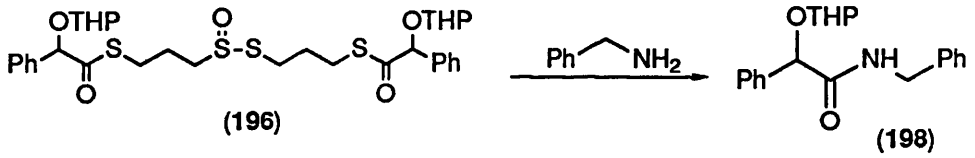
α-[(Tetrahydro-2*H*-pyran-2-yl)oxy] phenyl methyl acetate, (197).



(195) (197)

Pyridine (0.12ml, 1.46mmol) was added to a stirred solution of (**195**) (0.125g, 0.365mmol) in dry CH_2Cl_2 (5ml) under nitrogen. The solution was cooled to 0 °C and trifluoroacetic anhydride (0.054ml, 0.401mmol) added. Stirring was continued at 0 °C for 15 mins. Sodium methoxide (0.55g, 10.2mmol) was then added as a solution in methanol (3ml). Stirring was continued at 0 °C for a further 15 mins. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 5-10% EtOAc/petrol as the eluant afforded (**197**) as a pale yellow gum, (0.062g, 73%), Rf (20% EtOAc/petrol) 0.6; δ_H[136,138] ($CDCl_3$) 7.26-7.48 (5H, m, Ph), 5.33[a] (1H, s, PhC<u>H</u>), 5.25[b] (1H EtOAc/petrol) 0.6; δ_H[136,138] ($CDCl_3$) 7.26-7.48 (5H, m, Ph), 5.33[a] (1H, s, PhC<u>H</u>), 5.25[b] C<u>H</u> (1H, s, PhC<u>H</u>), 4.89[a] (1H, t, *J* 2.6, OC<u>H</u>O), 4.58[b] (1H, t, *J* 3.5, OC<u>H</u>O), 4.00-3.40 (5H, m,

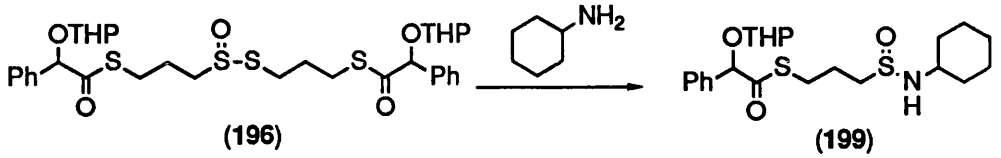
<u>α-[(Tetrahydro-2*H*-pyran-2-yl)oxyl-*N*-Benzylphenylacetamide, (198).</u>



To a solution of (**196**) (0.103g, 0.154mmol) in dry methanol (1ml), under nitrogen, was added benzylamine (0.05g, 0.463mmol). The mixture was stirred at room temperature for 48hrs. The solvents were then evaporated. Chromatography on silica gel with 10-40% EtOAc/petrol as the eluant afforded (**198**) as a pale yellow gum, (0.83g, 83%), Rf (50% EtOAc/petrol) 0.45; υ_{max} (Liq. film)/ cm^{-1} 3420 (N-H), 1740 (C=O); δ_H[136] ($CDCl_3$) 7.49-7.23 (10H and 1H[a], m, 2xPh and NH[a]), 5.25[b] (1H, s, C<u>H</u>Ph), 5.23[a] (1H, s, C<u>H</u>Ph), 4.85[b] (1H, m, OCHO), 4.56-4.40 (2H and 1H[a], m, PhC<u>H</u>$_2$ and OCHO[a]), 3.82[b] (2H, m, C<u>H</u>$_2$O), 3.52[a] (2H, m, C<u>H</u>$_2$O), 1.92-1.35 (6H, m, 3x CH_2); δ_C ($CDCl_3$) 171.2[b] (C=O), 70.6[a] (C=O), 138.2[a] (Ar), 138.1[b] (Ar), 137.8[b] (Ar), 137.0[a] (Ar), 128.7[c] (Ar), 128.6[c] (Ar), 128.5[c] (Ar), 128.3[c] (Ar), 128.0[c] (Ar), 127.5[c] (Ar), 127.45[c] (Ar), 127.40[c] (Ar), 127.3[c] (Ar), 126.6[c] (Ar), 98.1[b] (O<u>C</u>HO), 96.3[a] (O<u>C</u>HO), 78.3[b] (C<u>H</u>Ph), 77.4[a] (C<u>H</u>Ph), 63.0[a] (C<u>H</u>$_2$Ph), 62.2[b] (C<u>H</u>$_2$Ph), 42.9[a] (O<u>C</u>H$_2$), 36.6[b] (O<u>C</u>H$_2$), 30.5[b] (CH_2, THP), 30.3[a] (CH_2, THP), 25.1[a] (CH_2,

THP), 24.6[b] (CH_2, THP), 19.6[a] (CH_2, THP), 18.8[b] (CH_2, THP); m/z (EI) 325 (M^+, 30%), 241 (60), 85 (100).

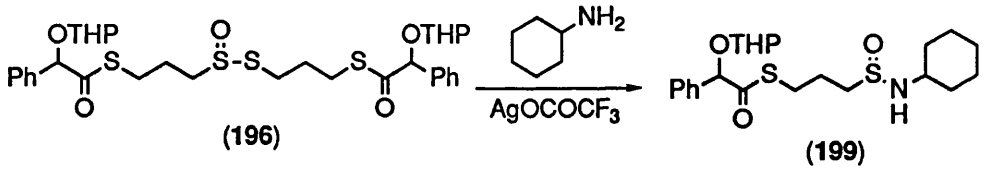
S-[3-(N-Cyclohexylsulphinamide)propyl]α-[(Tetrahydro-2H-pyran-2-yl)oxy]phenylthioacetate, (199).



(196) (199)

To a solution of (**196**) (0.107g, 0.160mmol) in dry methanol (1ml), under nitrogen, was added cyclohexylamine (0.048g, 0.481mmol). The mixture was stirred at room temperature for 48hrs. The solvents were then evaporated. Chromatography on silica gel with 10-40% EtOAc/petrol as the eluant afforded (**199**) as a pale yellow gum, (0.017g, 24%), Rf (20% EtOAc/petrol) 0.57; υ_{max} (Liq. film)/ cm^{-1} 3460 (N-H), 1710 (C=O); δ_H[136] ($CDCl_3$) 7.54-7.3 (6H, m, Ph and NH), 5.28[a] (1H, s, C<u>H</u>Ph), 5.26[b] (1H, s, C<u>H</u>Ph), 4.92[a] (1H, m, OC<u>H</u>O), 4.65[b] (1H, m, OC<u>H</u>O), 3.98[a] (1H, m, HC<u>H</u>O), 3.53 (2H[b] and 1H[a], m, $C\underline{H}_2O$[b] and <u>H</u>CHO[a]), 3.21 (1H, m, NC<u>H</u>), 2.93 (2H, m, O=CSC<u>H</u>$_2$), 2.70 (2H, m, $C\underline{H}_2$S=O), 2.05-.10 (18H, m, 5x CH_2 cyclohexyl, 3xCH_2 THP and $SCH_2C\underline{H}_2CH_2S$).

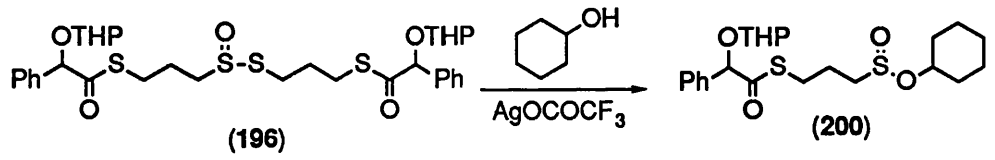
S-[3-(N-Cyclohexylsulphinamide)propyl]α-[(Tetrahydro-2H-pyran-2-yl)oxy]phenylthioacetate, (199).



(196) (199)

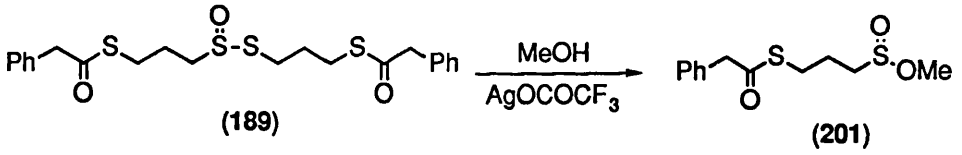
To a solution of (**196**) (0.10g, 0.150mmol) in dry THF (1ml), under nitrogen, was added cyclohexylamine (0.045g, 0.450mmol) and silvertrifluoroacetate (0.73g,0.330mmol). The mixture was stirred at room temperature for 35 mins. The solvents were then evaporated. Chromatography on silica gel with 20-60% EtOAc/petrol as the eluant afforded (**199**) as a pale yellow gum, (0.04g, 61%). See above for physical data.

S-[3-(Cyclohexylsulphinate)propyl]α-[(Tetrahydro-2*H*-pyran-2-yl)oxy]phenylthioacetate. (200).



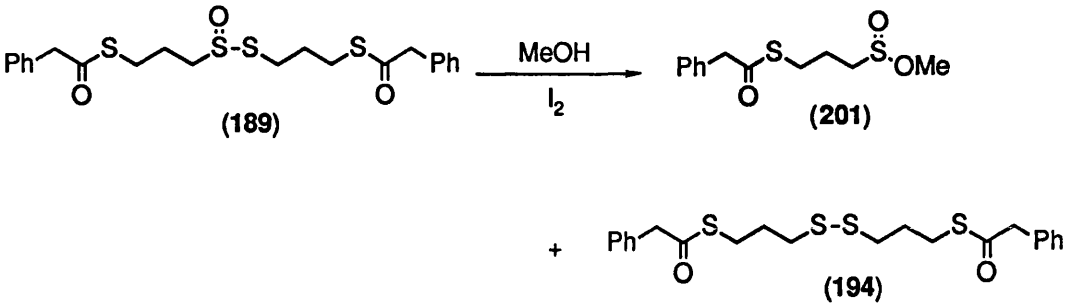
To a solution of (**196**) (0.10g, 0.150mmol) in dry THF (1ml), under nitrogen, was added cyclohexanol (0.045g, 0.450mmol) and silvertrifluoroacetate (0.132g,0.600mmol). The mixture was stirred at room temperature for 75 mins. The solvents were then evaporated. Chromatography on silica gel with 10-25% EtOAc/petrol as the eluant afforded (**200**) as a pale yellow gum, (0.60g, 91%), Rf (20% EtOAc/petrol) 0.26; υ_{max} (Liq. film)/ cm^{-1} 1690 (C=O); δ_H[136] ($CDCl_3$) 7.52-7.27 (5H, m, Ph), 5.27 (1H, m, PhC<u>H</u>), 4.93[a] (1H, br.s, OC<u>H</u>O), 4.66[b] (1H, br.s, OC<u>H</u>O), 4.17 (1H, m, CH(cyclohexyl)), 3.99[a] (1H, m, O<u>H</u>CH), 3.60[b] (2H, m, OCH_2), 3.48[a] (1H, m, OHC<u>H</u>), 2.95 (2H, m, CH_2S), 2.74 (2H, m, CH_2S), 2.07-1.05 (18H, m, 5x CH_2 cyclohexyl, 3xCH_2 THP and $SCH_2C\underline{H}_2CH_2S$).

S-[3-(Methylsulphinate)propyl]phenylthioacetate. (201).



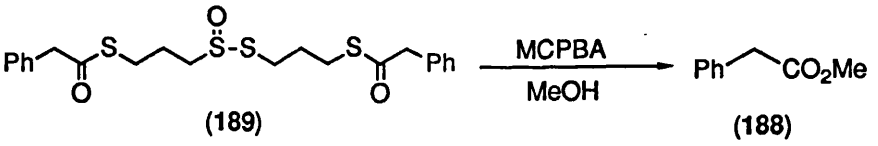
To a solution of (**189**) (0.10g, 0.214mmol) in dry THF (1ml), under nitrogen, was added methanol (0.027g, 0.857mmol) and silvertrifluoroacetate (0.142g,0.643mmol). The mixture was stirred at room temperature for 45 mins. The solvents were then evaporated. Chromatography on silica gel with 10-20% EtOAc/petrol as the eluant afforded (**201**) as a pale yellow gum, (0.038g, 65%), Rf (20% EtOAc/petrol) 0.42; υ_{max} (Liq. film)/ cm^{-1} 1690 (C=O); δ_H ($CDCl_3$) 7.40-7.20 (5H, m, Ph), 3.85 (2H, s, CH_2Ph), 3.76 (3H, s, OCH_3), 2.98 (2H, t, *J* 7.5, CH_2SCO), 2.76 (2H, m, CH_2SO), 1.98 (2H, pent, *J* 7.5, $CH_2C\underline{H}_2CH_2$); δ_C ($CDCl_3$) 196.6 (C=O), 133.4 (Ar), 129.6 (2x Ar), 128.7 (Ar), 127.5 (Ar), 55.2 (CH_2S or $PhCH_2$), 54.6 (OCH_3), 50.5 (CH_2S or $PhCH_2$), 28.1 (CH_2S or $PhCH_2$), 21.4 ($CH_2C\underline{H}_2CH_2$); m/z (EI) 272 (M^+, 50%), 212 (45), 192 (35), 136 (30), 90 (100).

S-[3-(Methylsulphinate)propyl]phenylthioacetate, (201) and Bis-(3-phenylacetylthio)propyl disulphide, (194).



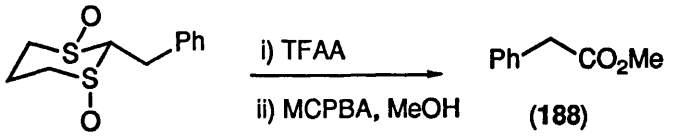
To a solution of (**189**) (0.092g, 0.197mmol) in CH_2Cl_2 (2ml), under nitrogen, at 0 °C, were added methanol (0.057g, 1.77mmol) and iodine (0.023g, 0.089mmol). Stirring was continued for 1 hr. The reaction mixture was then poured into aqueous saturated $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 10-20% EtOAc/petrol as the eluant afforded (**201**) (0.037g, 69%), see above for analytical details. Continued elution of the column also afforded (**194**) (0.035g, 78%), see above for analytical details.

Methyl phenyl acetate, (188).



To a solution of (**189**) (0.10g, 0.214mmol) in CH_2Cl_2 (1.5ml), at -78 °C, were added methanol (0.069g, 2.14mmol) and a 0.29M solution of MCPBA, in CH_2Cl_2, (4.44ml, 1.29mmol). The mixture was stirred at -78 °C-room temperature for 3 hrs. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 10% EtOAc/petrol as the eluant afforded (**188**) (0.033g, 51%), see above for analytical details.

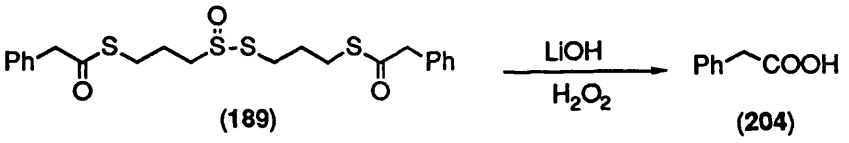
Methyl phenyl acetate, (188).



(187) (188)

Pyridine (0.13ml, 1.65mmol) was added to a stirred solution of (**187**) (0.10g, 0.413mmol) in dry CH_2Cl_2 (2.5ml) under nitrogen. The solution was cooled to 0 °C and trifluoroacetic anhydride (0.064ml, 0.454mmol) added. Stirring was continued at 0 °C for 15 mins. Methanol (0.17ml, 4.13mmol) and a 1.20M solution of MCPBA, in CH_2Cl_2, (2.1ml, 2.48mmol) were then added. Stirring was continued at 0 C for 30 mins. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 5-10% EtOAc/petrol as the eluant afforded methyl phenyl acetate (**188**) (0.009g, 15%), see above for analytical details.

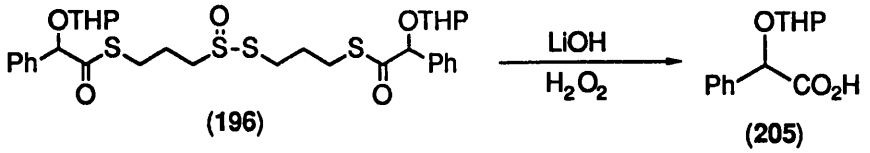
Phenyl acetic acid, (204).



(189) (204)

To a solution of (**189**) (0.105g, 0.225mmol) in THF (3ml) and water (1ml), at 0 °C, were added a 30% solution of H_2O_2 (0.3ml, 2.6 mmol) and lithium hydroxide (0.054g, 1.29mmol). The mixture was stirred for 90 mins. The reaction was quenched by addition of 1.5M Na_2SO_3(aq) solution (1.9ml, 2.83mmol). The THF was evaporated. The aqueous residue was diluted with water (10ml), and extracted with CH_2Cl_2(x3). Combined organic extracts were extracted with aqueous saturated $NaHCO_3$ solution (x2). Combined aqueous layers were acidified by addition of concerntrated HCl to pH 1-2. The acidified aqueous phase was then extracted with CH_2Cl_2 (x3). Combined organic extracts were dried ($MgSO_4$) and evaporated to give phenyl acetic acid, (**204**) (0.033g, 54%); Rf (50% EtOAc/petrol) 0.34; δ_H[140] ($CDCl_3$) 8.75 (1H, br.s, $CO_2\underline{H}$), 7.29 (5H, m, Ph), 3.64 (2H, s, $C\underline{H}_2Ph$).

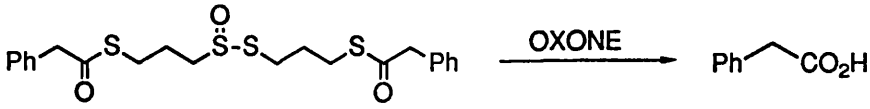
α-[(Tetrahydro-2*H*-pyran-2-yl)oxy]phenyl acetic acid, (205).



(196) (205)

To a solution of (**196**) (0.111g, 0.166mmol) in THF (3ml) and water (1ml), at 0 °C, were added a 30% solution of H_2O_2 (0.23ml, 2.0 mmol) and lithium hydroxide (0.042g, 0.99mmol). The mixture was stirred for 90 mins. The reaction was quenched by addition of 1.5M Na_2SO_3(aq) solution (1.5ml, 2.20mmol). The THF was evaporated. The aqueous residue was diluted with water (10ml), and extracted with CH_2Cl_2(x3). Combined organic extracts were extracted with aqueous saturated $NaHCO_3$ solution (x2). Combined aqueous layers were acidified by addition of concerntrated HCl to pH 1-2. The acidified aqueous phase was then extracted with CH_2Cl_2 (x3). Combined organic extracts were dried ($MgSO_4$) and evaporated to give mandelic acid, (**205**) (0.033g, 54%); Rf (50% EtOAc/petrol) 0.40; δ_H[136] ($CDCl_3$) 7.52-7.34 (5H, m, Ph), 7.00 (1H, br.s, $CO_2\underline{H}$), 5.33[b] (1H, s, C<u>H</u>Ph), 5.26[a] (1H, s, C<u>H</u>Ph), 4.91[b] (1H, t, *J* 5.6, OC<u>H</u>O), 4.61[a] (1H, t, *J* 5.6, OC<u>H</u>O), 3.95[b] (1H, m, O<u>H</u>CH), 3.68[B] (1H, M, OHC<u>H</u>), 3.50[a] (2H, m, OC<u>H</u>$_2$), 1.95-1.40 (6H, m, $CH_2CH_2CH_2$).

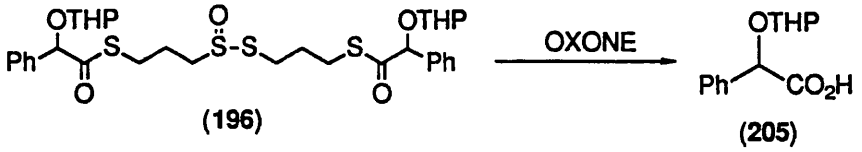
Phenyl acetic acid, (204).



(189) (204)

To a solution of (**189**) (0.10g, 0.214mmol) in acetone (2ml) was added a solution of OXONE (0.660g, 1.07mmol), in water (2ml). The mixture was stirred at room temperature for 16 hrs. The acetone was evaporated. The aqueous residue was acidified to pH 1 by addition of concerntrated HCl and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give phenyl acetic acid, (**204**) (0.056g, 96%), see above for analytical details.

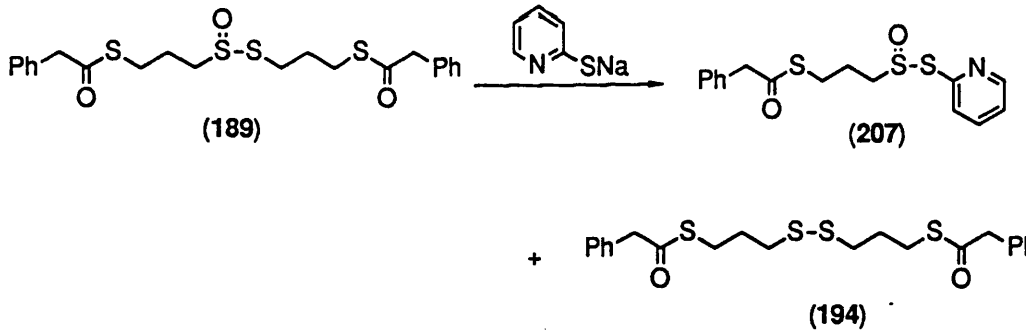
α-[(Tetrahydro-2*H*-pyran-2-yl)oxy]phenyl acetic acid, (205).



(196) (205)

To a solution of (**196**) (0.10g, 0.150mmol) in acetone (3ml) was added a solution of OXONE (0.550g, 0.90mmol), in water (3ml). The mixture was stirred at room temperature for 16 hrs. The acetone was evaporated. The aqueous residue was acidified to pH 1 by addition of concerntrated HCl and extracted with CH_2Cl_2 (x3). Combined organic extracts were extracted with aqueous saturated $NaHCO_3$ solution (x2). Combined basic extracts were washed with CH_2Cl_2, acidified to pH 1 by addition of concerntrated HCl and extracted with CH_2Cl_2 (x3). Combined organic extracts were dried ($MgSO_4$) and evaporated to give (**205**) (0.015g, 21%), see above for analytical details.

S-[3-(2-Pyridylthiosulphinyl)propyl]phenylthioacetate, (207) and Bis-(3-phenylacetylthio)propyl disulphide, (194).

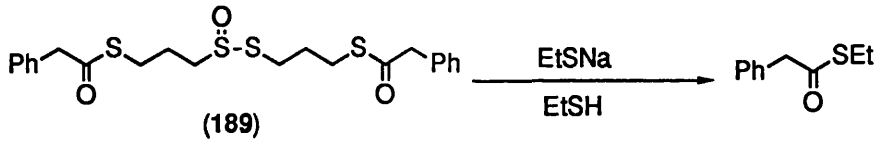


(189) (207) (194)

To a solution of 2-mercaptopyridine (0.36g, 3.21mmol) in methanol (0.5ml), in a dried flask under nitrogen at 0 °C, was added a 1M solution of sodium methoxide in methanol (1.07ml,1.07mmol). The mixture was stirred at 0 °C for 10 mins. A solution of (**189**) (0.10g, 0.214mmol) in CH_2Cl_2 (1.5ml) was then added and stirring continued for a further 30 mins at 0 °C. The solvents were then evaporated. Chromatography on silica gel with 10% EtOAc/petrol as the eluant afforded (**194**) (0.042g, 87%), see above for analytical data. Continued elution of the column afforded (**207**) as a pale yellow gum, (0.069g, 92%), Rf (20% EtOAc/petrol) 0.45; υ_{max} (Liq. film)/ cm^{-1} 1540 (C=O); δ_H ($CDCl_3$) 8.46 (1H, m, py),

7.65 (2H, m, py), 7.30 (5H, m, Ph), 7.08 (1H, m, py), 3.82 (H, s, $PhCH_2$), 2.96 (2H, t, *J* 6.3, SCH_2), 2.81 (2H, t, *J* 6.3, CH_2S), 1.95 (2H, pent, *J* 6.3, $CH_2\underline{CH_2}CH_2$); δ_C ($CDCl_3$) 197.1 (C=O), 160.0 (Ar), 149.7 (Ar) 137.0 (Ar), 133.5 (Ar), 129.6 (2x Ar), 128.7 (2xAr), 127.5 (Ar), 120.7 (Ar), 119.7 (Ar), 50.5 (SCH_2), 37.4 (SCH_2), 28.6 ($PhCH_2$ or $CH_2\underline{CH_2}CH_2$), 27.2 ($PhCH_2$ or $CH_2\underline{CH_2}CH_2$); m/z (EI) 351 (M^+, 1%), 335 (5), 216 (10), 111 (40), 91 (100).

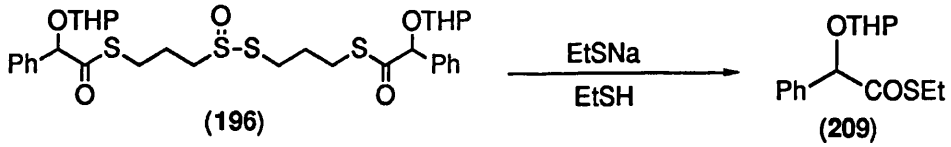
S-Ethyl phenyl thioacetate, (208).



(189) (208)

To a solution of (**189**) (0.10g, 0.214mmol) in ethanethiol (1.6ml), in a dried flask under nitrogen at room temperature, was added sodium ethanethiolate (0.072g, 0.857mmol). Stirring was continued for 16 hrs. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 5-10% EtOAc/petrol as the eluant afforded (**208**) (0.074g, 96%) as a pale yellow oil, Rf (10% EtOAc/petrol) 0.59; δ_H[139] ($CDCl_3$) 7.31 (5H, m, Ph), 3.82 (2H, s, CH_2Ph), 2.86 (2H, q, *J* 7.8, $S\underline{CH_2}CH_3$), 1.22 (3H, t, *J* 7.8, $SCH_2\underline{CH_3}$).

S-Ethyl α(RS) -[(tetrahydro-2*H*-pyran-2-yl)oxy]phenyl thioacetate, (209).

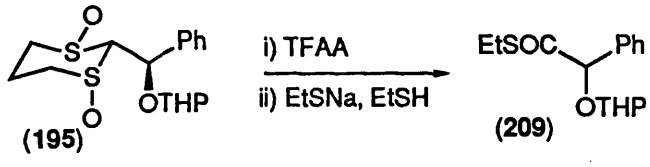


(196) (209)

To a solution of (**196**) (0.145g, 0.217mmol) and ethanethiol (0.16ml, 2.17mmol), in THF (2ml), in a dried flask under nitrogen at room temperature, was added sodium ethanethiolate (0.091g, 1.09mmol). Stirring was continued for 2.5 hrs. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on

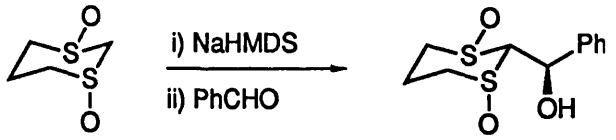
silica gel with 2.5-5% EtOAc/petrol as the eluant afforded (**209**) (0.118g, 97%) as a pale yellow oil, Rf (10% EtOAc/petrol) 0.41; υ_{max} (Liq. film)/ cm^{-1} 2940, 1770 (C=O); δ_H[136] ($CDCl_3$) 7.60-7.25 (5H, m, Ph), 5.30[a] (1H, s, CHPh), 5.27[b] (1H, s, CHPh), 4.95[a] (1H, t, *J* 3.8, OCHO), 4.68[b] (1H, t, *J* 3.8, OCHO), 4.05[a] (1H, m, OCHCH), 3.73-3.50[b] (1H, m, OCH_2), 3.45[a] (1H, m, OHCH), 2.84[a] (2H, q, *J* 7.5, SCH_2), 2.81[b] (2H, q, *J* 7.5, SCH_2), 2.15-1.40 (6H, m, 3x CH_2), 1.23[b] (3H, t, *J* 7.5, SCH_2CH_3), 1.21[a] (3H, t, *J* 7.5, SCH_2CH_3); δ_C[136] ($CDCl_3$) 202.0[a] (C=O), 200.0[b] (C=O), 137.1[a] (Ar), 136.6[b] (Ar), 128.8[c] (Ar), 128.7[c] (Ar), 128.4 [c](Ar), 127.6[c] (Ar), 127.1[c] (Ar), 126.8[c] (Ar), 98.1[a] (OCHO), 95.3[b] (OCHO), 82.1[a] (CHPh), 81.7[b] (CHPh), 62.0 (OCH_2), 30.2[a] (SCH_2), 30.0[b] (SCH_2), 25.4[a] (CH_2), 25.2[b] (CH_2), 23.4[b] (CH_2), 22.7[a] (CH_2), 18.6[a] (CH_2), 18.5[b] (CH_2), 14.4 (CH_3); m/z (EI) 280 (M^+, 30%), 149 (60), 113 (60), 71 (75), 57 (100), 43 (40).

***S*-Ethyl α(RS)-[(tetrahydro-2*H*-pyran-2-yl)oxy]phenyl thioacetate, (209).**



Pyridine (0.086ml, 1.06mmol) was added to a stirred solution of (**195**) (0.091g, 0.266mmol) in dry CH_2Cl_2 (5ml) under nitrogen. The solution was cooled to 0 °C and trifluoroacetic anhydride (0.045ml, 0.319mmol) added. Stirring was continued at 0 °C for 15 mins. A suspension of sodium ethanethiolate (0.16g, 1.86mmol) and ethanethiol (0.25g, 3.99mmol), in THF (2ml), was then added. Stirring was continued at 0 °C-room temperature for a further 5 hrs. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 0-2.5% EtOAc/petrol as the eluant afforded thiol ester, (**209**) as a pale yellow gum, (0.055g, 74%), analysis as above.

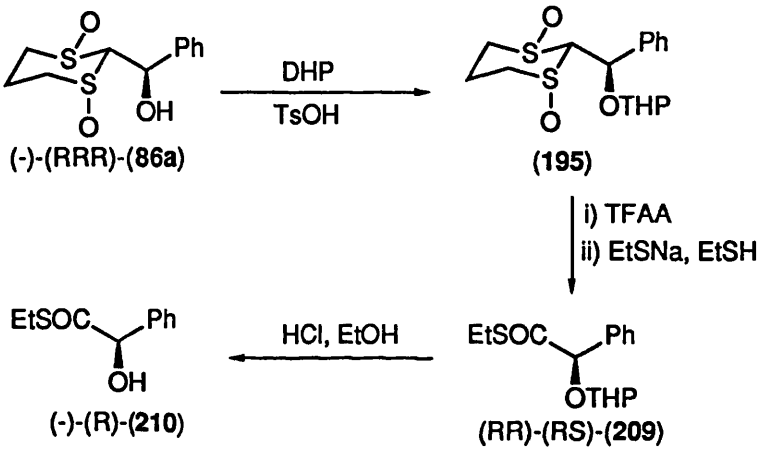
(-)-1-(R)-3-(R)-α-(R)-α-Phenyl-1,3-dithiane-1,3-dioxide-2-methanol, (-)-(RRR)-(86a).



(+)-(63) (-)-(RRR)-(86a)

Using the same procedure as that used for the synthesis of racemic (**86a**), homochiral dithiane dioxide (+)-(**63**) (0.4g, 2.63 mmol) gave (-)-(RRR)-(**86a**) (0,364g, 54%), m.p. 164-6 °C; δ_H ($CDCl_3$) as (+/-)-(**86a**), $[\alpha]_D$ (c=0.5, MeOH) -97.2°.

(−)-α-(R)-*S*-Ethyl α-hydroxyphenyl thioacetate, (-)-(R)-(210).

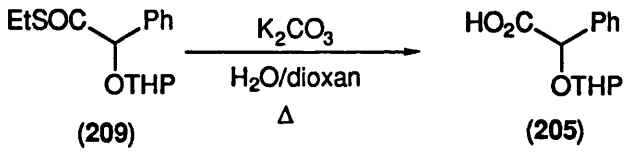


(-)-(RRR)-(86a) (195)

(-)-(R)-(210) (RR)-(RS)-(209)

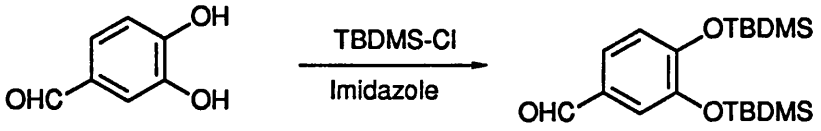
Using the procedures for the synthesis of racemic (**195**) and (**209**) homochiral (-)-(RRR)-(**86a**) (0.196g, 0.759 mmol) gave (RR)-(RS)-(**209**) (0.124g, 58%). The *O*-protected thiolester (RR)-(RS)-(**209**) (0.113g, 0.403mmol) was dissolved in a 10% v/v 2M HCl (aq) in ethanol and the mixture stirred for 16 hrs. The solvents were evaporated, azeotroping with toluene (x2). Chromatography on silica gel with 5-10% EtOAc/petrol as the eluant afforded thiol ester, (-)-(R)-(**210**) as a waxy solid (0.069g, 87%). An analytical was recrystallized from EtOAc/petrol, m.p. 52-3 °C Rf (10% EtOAc/petrol) 0.21; (Found: C, 61.1; H, 6.00. Requires for $C_{10}H_{12}O_2S$: C, 61.2; H, 6.16%); υ_{max} (Liq. film)/ cm^{-1} 3500-3300 (O-H), 1750 (C=O); δ_H ($CDCl_3$) 7.40 (5H, m, Ph), 5.22 (1H, s, C<u>H</u>Ph), 3.16 (1H, br.s, OH), 2.90 (2H, m, S<u>C</u>H_2CH_3), 1.25 (3H, t, *J* 7.5, $SCH_2C\underline{H}_3$); δ_C ($CDCl_3$) 202.0 (C=O), 138.2 (Ar), 128.9 (Ar), 128.8 (2x Ar), 127.1 (2x Ar), 80.0 (<u>C</u>HPh), 23.5 (S<u>C</u>H_2CH_3), 14.4 ($SCH_2\underline{C}H_3$); m/z (EI) 197 (M^+, 60%), 151 (100), 107 (70), 79 (55), $[\alpha]_D$ (c=0.69, $CHCl_3$) -216.2°.

α-[(Tetrahydro-2*H*-pyran-2-yl)oxy]phenyl acetic acid, (205).



To a solution of the thiol ester (**209**) (0.265g, 0.945 mmol) in 1,4-dioxan (2ml) and water (2ml) was added potassium carbonate (0.196g, 1.42 mmol). The mixture was heated under reflux for 18 hrs. The mixture was concerntrated *in vacuo* and the aqueous residue diluted with water and extracted with CH_2Cl_2. The aqueous phase was acidified to pH 1 by addition of 2M HCl and extracted with CH_2Cl_2 (x3). Combined organic extracts were dried ($MgSO_4$) and evaporated to give (**205**) (0.188g, 84%) analysis as above.

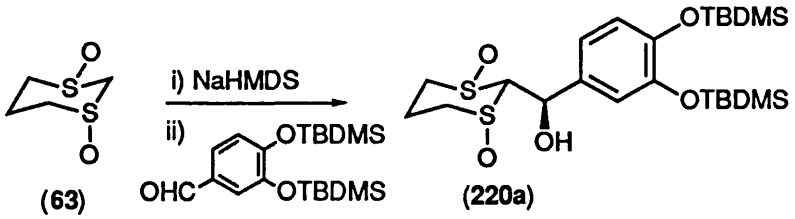
3,4-Di-*tert*-butyldimethylsilyloxybenzaldehyde, (219).



(219)

To a solution of 3,4-dihydoxybenzaldehyde (1.0g, 7.24mmol) in dry CH_2Cl_2 in a dried flask, under nitrogen were added *tert*-butylchlorodimethylsilane (2.4g, 15.9mmol) and imidazole (1.23g, 18.1mmol). The reaction mixture was stirred at room temperature for 48 hrs. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 0-10% EtOAc/petrol as the eluant afforded (**219**) (1.50g, 56%), Rf (20% EtOAc/petrol) 0.8; δ_H[141] ($CDCl_3$) 9.80 (1H, s, C<u>H</u>O), 7.40-7.33 (2H, m, 2x Ar), 6.94 (1H, d, *J* 8.8, Ar), 0.992 (9H, s, (C<u>H</u>$_3$)$_3$CSi), 0.989 (9H, s, (C<u>H</u>$_3$)$_3$CSi), 0.25 (6H, s, 2x C<u>H</u>$_3$Si), 0.22 (6H, s, 2x C<u>H</u>$_3$Si).

1-(RS)-3-(RS)-α-(RS)-α-(3,4-Di-*tert*-butyldimethylsilyloxyphenyl)-1,3-dithiane-1,3-dioxide-2-methanol, (220a).

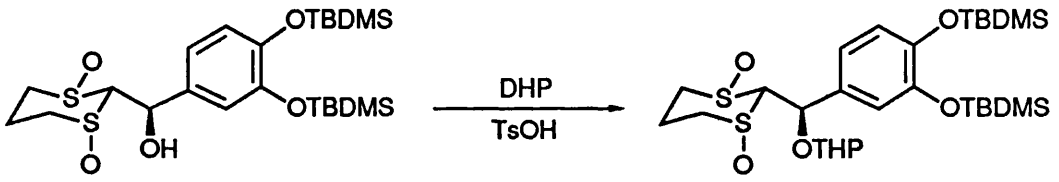


(63) **(220a)**

Dithiane dioxide (**63**) (0.311g, 2.05mmol) was dissolved in pyridine (15ml) with warming and then diluted with THF (9ml) before cooling to 0 °C, under nitrogen. To this was added a 1.0M solution of NaHMDS in THF (2.45ml, 2.45mmol). Stirring was continued at 0 °C for 0.5hr. The aldehyde (**219**) was then added (0.9g, 2.45mmol), as a solution in pyridine (2ml). Stirring was continued for 10 mins at 0 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (51ml) and aqueous HCl (2M, 5.1ml, 10.2mmol) at 0 °C. The solvents were then evaporated under vacuum. Chromatography on silica gel with 25-50% acetone/EtOAc as the eluant afforded (**220a**) (0.59g, 56%). An analytical sample was recrystallized from EtOAc m.p. 141 °C; Rf (acetone) 0.58; (Found: C,

52.7; H, 8.48. Requires for $C_{23}H_{42}O_5S_2Si_2$: C, 53.2; H, 8.16%); υ_{max} (Nujol)/ cm^{-1} (S-O); δ_H (DMSO) 6.98 (1H, s, Ar), 6.80 (2H, s, 2x Ar), 5.91 (1H, d, *J* 4.4, OH), 5.31 (1H, dd, *J* 4.4 and 4.4, α-H), 4.02 (1H, d, *J* 4.4, 2-H), 3.45 (1H, dm, *J* 11.6, 4-H), 3.15 (1H, dm, *J* 11.6, 4-H), 2.90-2.70 (2H, m, 2x 6-H), 2.45 (1H, m, 5-H), 2.13 (1H, dm, *J* 16, 5-H), 0.90 (18H, s, 2x ($C\underline{H}_3)_3CSi$), 0.12 (12H, s, 4x $C\underline{H}_3Si$); δ_C ($CDCl_3$) 147.8 (Ar), 131.6 (2x Ar), 121.3 (Ar), 119.0 (Ar), 118.9 (Ar), 78.3 (C-2), 70.3 (COH), 48.6 (C-4 or C-6), 45.5 (C-4 or C-6), 25.9 (2x ($\underline{C}H_3)_3CSi$), 18.4 (2x $(CH_3)_3\underline{C}Si$), 14.0 (C-5), -4.1 (4x $\underline{C}H_3Si$).

1-(RS)-3-(RS)-α-(RS)-α-(3,4-Di-*tert*-butyldimethylsilyloxyphenyl)-1,3-dithiane-1,3-dioxide-2-[(tetrahydro-2*H*-pyran-2-yl)oxy]methane, (221).

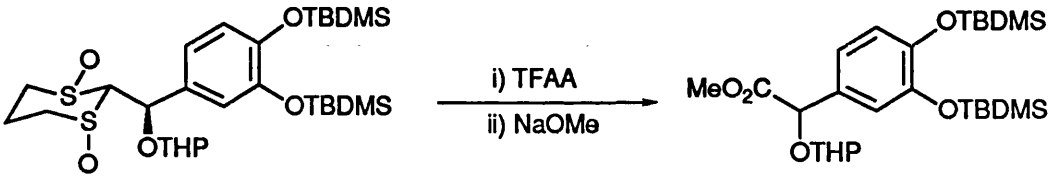


(220a) (221)

The alcohol (**220a**) (2.50g, 4.81mmol) was dissolved in dry CH_2Cl_2 (80ml), under nitrogen at 0 °C. Dihydropyran (2.20ml, 24.1mmol) and *p*-toluene sulphonic acid (37mg, 0.193mmol) were added and stirring continued at 0 °C for 90 mins. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 10-40% acetone/EtOAc as the eluant afforded (**221**) (2.70g, 93%). An analytical sample was recrystallized from EtOAc/petrol, m.p. 97-99 °C; Rf (50% acetone/petrol) 0.39; υ_{max} (Nujol)/ cm^{-1} 1040 (S-O); δ_H[136] ($CDCl_3$) 7.10-6.80 (3H, m, Ar), 5.53[a] (1H, d, *J* 4.5, C$\underline{H}$OH), 5.41[b] (1H, d, *J* 4.1, C$\underline{H}$OH), 5.12[b] (1H, m, OCHO), 4.69[a] (1H, m, OCHO), 3.75-3.25 (4H, m, 4-H, OCH_2 and 2-H), 3.17 (1H, dm, *J* 15.0, 4-H), 2.90 (2H, m, 2x 6-H), 2.70 (1H, m, 5-H), 2.40 (1H, m, 5-H), 2.05-1.35 (6H, m, $CH_2CH_2CH_2$), 0.99 (18H, m, 2x $(CH_3)_3CSi$), 0.21 (12H, m, 2x $(CH_3)_2Si$); δ_C[136] ($CDCl_3$) 147.4[b] (Ar), 147.2[a] (Ar), 146.9[a] (Ar), 146.8[b] (Ar), 131.9[b] (Ar), 129.3[a] (Ar), 121.06[b] (Ar), 121.00[a] (Ar), 120.9[b] (Ar), 120.1[a] (Ar), 119.9[b] (Ar), 119.8[a] (Ar), 99.5[b] (OCHO), 93.9[a] (OCHO), 81.5[b] (COTHP), 80.9[a] (COTHP), 72.3[b] (C-2), 70.1[a] (C-2), 61.8[b] (C-4, C-6 or OCH_2), 61.5[a] (C-4, C-6 or OCH_2), 50.2[a] (C-4, C-6 or OCH_2), 49.9[b] (C-4, C-6 or OCH_2), 45.3[a] (C-4, C-6 or OCH_2), 44.9[b] (C-4,

C-6 or OCH_2), 30.0[a] (CH_2, THP), 29.8[b] (CH_2, THP), 25.9[c] ($SiC(\underline{C}H_3)_3$), 25.85[c] ($SiC(\underline{C}H_3)_3$), 25.80[c] ($SiC(\underline{C}H_3)_3$), 25.4[a] (CH_2, THP), 25.2[b] (CH_2, THP), 18.4[a] (CH_2, THP), 18.3[b] (CH_2, THP), 13.7[a] (C-5), 13.6[b] (C-5), -4.10[c] (CH_3Si), -4.13[c] (CH_3Si); *m/z* (FAB) 625 (M+Na, 30%), 501 (40), 437 (100), 267 (65).

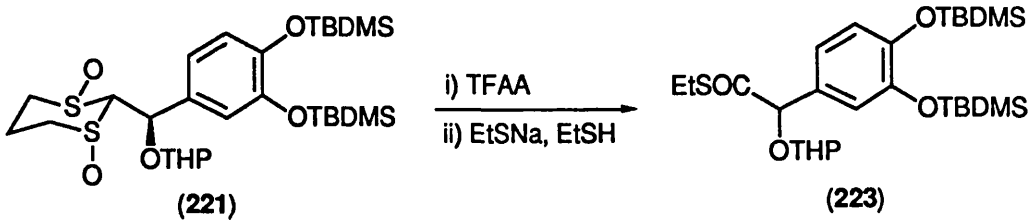
α-[(Tetrahydro-2*H*-pyran-2-yl)oxyl-methyl-(3,4-di-*tert*-butyldimethylsilyloxyphenyl) acetate, (222).



(221) (222)

Pyridine (0.54ml, 6.63mmol) was added to a stirred solution of (**221**) (1.0g, 1.66mmol) in dry CH_2Cl_2 (30ml) under nitrogen. The solution was cooled to 0 °C and trifluoroacetic anhydride (0.26ml, 1.82mmol) added. Stirring was continued at 0 °C for 15 mins. Sodium methoxide (0.63g, 11.6mmol) was then added as a solution in methanol (15ml). Stirring was continued at 0 °C-room temperature for a further 7 hrs. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 0-10% EtOAc/petrol as the eluant afforded (**222**) as a pale yellow gum, (0.34g, 40%), Rf (20% EtOAc/petrol) 0.60; υ_{max} (Liq. film)/ cm^{-1} ; δ_H[136] ($CDCl_3$) 6.97-6,76 (3H, m, Ar), 5.20[a] (1H, s, ArC<u>H</u>), 5.12[b] (1H, s, ArC<u>H</u>), 4.84[a] (1H, t, *J* 2.9, OCHO), 4.55[b] (1H, t, *J* 3.6, OCHO), 3.93[a] (1H, m, O<u>H</u>CH), 3.76[a] (1H, m, OHC<u>H</u>), 3.70 (3H, s, CO_2CH_3), 3.49[b] (2H, m, OCH_2), 2.00-1.41 (6H, m, $CH_2CH_2CH_2$), 0.98 (18H, s, 2x $(CH_3)_3CSi$), 0.19 (12H, s, 2x $(CH_3)_2Si$); m/z (EI) 510 (M^+, 15%), 453 (15), 237 (100), 86 (95), 73 (90), 57 (15).

S-Ethyl-α-[(tetrahydro-2*H*-pyran-2-yl)oxy]-(3,4-di-*tert*-butyldimethylsilyloxyphenyl) thioacetate, (223).



(221) (223)

Pyridine (0.16ml, 3.32mmol) was added to a stirred solution of (**221**) (0.50g, 0.829mmol) in dry CH_2Cl_2 (20ml) under nitrogen. The solution was cooled to 0 °C and trifluoroacetic anhydride (0.21ml, 0.995mmol) added. Stirring was continued at 0 °C for 15 mins. A suspension of sodium ethanethiolate (0.45g, 5.80mmol) and ethanethiol (0.77g, 12.4mmol), in THF (10ml), was then added. Stirring was continued at 0 °C-room temperature for a further 15 hrs. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 0-3% EtOAc/petrol as the eluant afforded thiol ester, (**223**) as a pale yellow gum, (0.41g, 91%), Rf (10% EtOAc/petrol) 0.41; υ_{max} (Liq. film)/ cm^{-1} 2900 (br), 1780 (SC=O); δ_H[136] ($CDCl_3$) 7.00-6.73 (3H, m, Ar), 5.12[b] (1H, s, PhC<u>H</u>), 5.08[a] (1H, s, PhC<u>H</u>), 4.86[b] (1H, t, *J* 3.8, OCHO), 4.62[a] (1H, t, *J* 4.5, OCHO), 4.00-3.38 (2H, m, OCH_2), 2.81 (2H, m, $SC\underline{H}_2CH_3$), 1.94-1.50 (6H, m, $CH_2CH_2CH_2$), 1.22 (3H, m, $SCH_2C\underline{H}_3$), 1.00 (18H, s, 2x $(C\underline{H}_3)_3CSi$), 0.23-0.18 (12H, m, 2x $(CH_3)_2Si$); δ_C[5] ($CDCl_3$) 202.0[b] (C=O), 200.3[a] (C=O), 174.3[c] (Ar), 146.9[c] (Ar), 130.9[c] (Ar), 130.2[c] (Ar), 129.3[c] (Ar), 128.8[c] (Ar), 121.2[c] (Ar), 120.7[c] (Ar), 120.0[c] (Ar), 119.6[c] (Ar), 97.8[b] (OCHO), 95.0[a] (OCHO), 61.9[a] (OCH_2), 61.8[b] (OCH_2), 30.2[a] (SCH_2), 30.0[b] (SCH_2), 26.0[c] ($(\underline{C}H_3)_3CSi$), 25.9[c] ($(\underline{C}H_3)_3CSi$), 25.4[a] (CH_2, THP), 25.3[b] (CH_2, THP), 22.6 (CH_2, THP), 18.6[b] (CH_2, THP), 18.5[a] (CH_2, THP), 14.4 ($\underline{C}H_3CH_2S$), -3.2 (2x $(\underline{C}H_3)_2Si$); m/z (EI) 540 (M^+, 1%), 509 (5), 439 (15), 411 (100).

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